

EXHIBIT 29



PART 6

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	15705172
	Filing Date	2017-09-14
	First Named Inventor	Stephen Donald WILTON
	Art Unit	1674
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AVN-008CN41

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Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
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21	6210892		2001-04-03	Bennett et al.	
22	6312900		2001-11-06	Dean et al.	
23	6391636		2002-05-21	Monia	
24	6451991		2002-09-17	Martin et al.	
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33	7163695	2007-01-16	Mixson
34	7250289	2007-07-31	Zhou
35	7314750	2008-01-01	Zhou
36	7468418	2008-12-23	Iversen et al.
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	8	2nd Expert Declaration of Dr. Erik Sontheimer ("2nd S Decl.") (Exhibit Number 1067 filed in interferences 106008, 106007 on December 23, 2014)	
	9	3rd Declaration of Erik J. Sontheimer, Ph.D. ("3rd S. Decl."), Pages 123, Exhibit Number 1186 filed in Interferences 106,007 and 106,008 on February 17, 2015.	

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36	AON PS1958 UPLC Data, Pages 2, Exhibit Number 1157 filed in Interferences 106,007 and 106,008 on February 16, 2015.
37	AON PS1959 Mass Spectrometry Data, Pages 5, Exhibit Number 1147 filed in Interferences 106,007 and 106,008 on February 16, 2015.
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39	AON PS1960 Mass Spectrometry Data, Pages 8, Exhibit Number 1148 filed in Interferences 106,007 and 106,008 on February 16, 2015.
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41	AON PS1961 Mass Spectrometry Data, Pages 5, Exhibit Number 1149 filed in Interferences 106,007 and 106,008 on February 16, 2015.
42	AON PS1961 UPLC Data, Pages 2, Exhibit Number 1160 filed in Interferences 106,007 and 106,008 on February 16, 2015.

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43	AON PS1962 Mass Spectrometry Data, Pages 7, Exhibit Number 1150 filed in Interferences 106,007 and 106,008 on February 16, 2015.
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45	AON PS1963 Mass Spectrometry Data, Pages 10, Exhibit Number 1151 filed in Interferences 106,007 and 106,008 on February 16, 2015.
46	AON PS1963 UPLC Data, Pages 2, Exhibit Number 1162 filed in Interferences 106,007 and 106,008 on February 16, 2015.
47	AON PS1964 Mass Spectrometry Data, Pages 13, Exhibit Number 1152 filed in Interferences 106,007 and 106,008 on February 16, 2015.
48	AON PS1964 UPLC Data, Pages 2, Exhibit Number 1163 filed in Interferences 106,007 and 106,008 on February 16, 2015.
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50	AON PS1965 UPLC Data, Pages 2, Exhibit Number 1164 filed in Interferences 106,007 and 106,008 on February 16, 2015.

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2	Hammond, Suzan M., et al., "PRO-051, an antisense oligonucleotide for the potential treatment of Duchenne muscular dystrophy," Curr. Opinion Mol. Therap., Vol. 12, No. 4, pp. 478-486 (2010), Exhibit Number 1121 filed in interferences 106,007 and 106,008 on February 13, 2015.
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4	Havenga et al., "Exploiting the Natural Diversity in Adenovirus Tropism for Therapy and Prevention of Disease," J. Virol., Vol. 76, No. 9, pp. 4612-4620 (May, 2002), Exhibit Number 1123 filed in interferences 106,007 and 106,008 on February 13, 2015.
5	HEASMAN, Janet, "Morpholino Oligos: Making Sense of Antisense?" Developmental Biology, Vol. 243:209-214 (2002)
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11	HUDZIAK, Robert M. et al., "Antiproliferative Effects of Steric Blocking Phosphorodiamidate Morpholino Antisense Agents Directed against c-myc," Antisense & Nucleic Acid Drug Development, Vol. 10:163-176 (2000) (Exhibit Number 1032 filed in interferences 106008, 106007 on November 18, 2014)

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14	International Patent Application No. PCT/AU2000/00693 ("Wraight"), published as WO 00/78341 on December 28, 2000, 201 pages, (Exhibit Number 2125 filed in interferences 106,007 and 106,008 on February 17, 2015.
15	International Preliminary Report on Patentability and Written Opinion for Application No. PCT/US2009/061960, 8 pages, dated April 26, 2011
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Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

23	International Search Report and Written Opinion of the International Searching Authority issued in International Patent Application No. PCT/US2014/029689, 8 pages, dated October 21, 2014
24	International Search Report and Written Opinion of the International Searching Authority issued in International Patent Application No. PCT/US2014/029766 dated October 21, 2014
25	International Search Report and Written Opinion, PCT/US2016/054534, dated January 17, 2017, 13 pages.
26	International Search Report for Application No. PCT/AU2005/000943, 5 pages, dated October 20, 2005
27	International Search Report for Application No. PCT/US01/14410, 5 pages, dated March 6, 2002
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37	Job Posting by Sarepta for "Scientist II, Muscle Biology" (2 pages), (Academisch Ziekenhuis Leiden Exhibit 1233, filed April 3, 2015 in Interference 106007 and 106008).
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See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

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Signature	/Amy E. Mandragouras, Esq./	Date (YYYY-MM-DD)	2017-09-22
Name/Print	Amy E. Mandragouras, Esq.	Registration Number	36,207

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1	Sarepta Briefing Information for the April 25, 2016 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, Eteplirsen Briefing Document, NDA 206488, 186 pages.
2	Sarepta Presentation at Peripheral and Central Nervous System Drugs Advisory Committee, April 25, 2016, 133 pages
3	Sarepta Press Release, Sarepta Issues Statement on Advisory Committee Outcome for Use of Eteplirsen in the Treatment of Duchenne Muscular Dystrophy, April 25, 2016, 2 pages
4	Sarepta Therapeutics Press Release, dated January 12, 2015, Exhibit Number 1119 filed in interferences 106,007 and 106,008 on February 17, 2015.
5	Sarepta Therapeutics, Advisory Committee Briefing Materials: Available for Public Release, "Peripheral and Central Nervous System Drugs Advisory Committee," Eteplirsen Briefing Document Addendum, NDA 206488, pages 1-9, dated January 22, 2016.
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7	Sarepta Therapeutics, Inc. News Release, "Sarepta Therapeutics Announces FDA Accelerated Approval of EXONDYS 51™ (eteplirsen) injection, an Exon Skipping Therapy to Treat Duchenne Muscular Dystrophy (DMD) Patients Amenable to Skipping Exon 51," September 19, 2016, 2 pages.
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12	Second Preliminary Amendment filed in US Application No. 13/550,210, 5 pages, dated January 3, 2013 (Exhibit Number 2062 filed in interferences 106008, 106013, 106007 on November 18, 2014)
13	Second Written Opinion for Application No. PCT/AU2010/001520, 7 pages, dated October 13, 2011
14	Semi Quantitative Lab-on-Chip Analysis of Second PCR Product, Pages 1, Exhibit Number 1183 filed in Interferences 106,007 and 106,008 on February 16, 2015.
15	Sequence Listing - Serial No. 13/550,210, as filed July 16, 2012 (9 pages), Exhibit Number 1205 filed in Interferences 106,007 and 106,008 on February 17, 2015.
16	Sequence of Exon 46 of Dystrophin Gene, 1 page
17	Sequence of Exon 51 of Dystrophin Gene, 1 page
18	Shabanpoor et al., "Bi-specific splice-switching PMO oligonucleotides conjugated via a single peptide active in a mouse model of Duchenne muscular dystrophy," Nucleic Acids Res., pp. 1-11 (December, 2014), Exhibit Number 1114 filed in interferences 106,007 and 106,008 on February 17, 2015.
19	SHAPIRO, Marvin B. et al., "RNA splice junctions of different classes of eukaryotes: sequence statistics and functional implications in gene expression," Nucleic Acids Research, Vol. 15(17):7155-7174 (1987)
20	SHERRATT, Tim G. et al., "Exon Skipping and Translation in Patients with Frameshift Deletions in the Dystrophin Gene," Am. J. Hum. Genet., Vol. 53:1007-1015 (1993)
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23	Siemens Healthcare Diagnostics, Inc. v. Enzo Life Sciences, Inc., 2013 WL 4411227, *11 [Parallel cite: U.S.D.C., D. Mass., Civil No. 10-40124-FDS], Decided Aug. 14, 2013 (12 pages); [Cited as: 2013 WL 4411227], Exhibit Number 1210 filed in Interferences 106,007 and 106,008 on February 17, 2015.
24	SIERAKOWSKA, Halina et al., "Repair of thalassemic human beta-globin mRNA in mammalian cells by antisense oligonucleotides," Proc. Natl. Acad. Sci. USA, Vol. 93:12840-12844 (1996)
25	Sontheimer et al., "Metal ion catalysis during group II intron self-splicing: parallels with the spliceosome," Genes & Development, Vol. 13, pp. 1729-1741 (1999), Exhibit Number 1195 filed in Interferences 106,007 and 106,008 on February 17, 2015.
26	Sontheimer et al., "Three Novel Functional Variants of Human U5 Small Nuclear RNA," Vol. 12, No. 2, pp. 734-746 (Feb., 1992), Exhibit Number 1194 filed in Interferences 106,007 and 106,008 on February 17, 2015.
27	SONTHEIMER, Erik J. et al., "Metal ion catalysis during splicing of premessenger RNA," Nature, Vol. 388:801-805 (1997) (Exhibit Number 1036 filed in interferences 106008, 106007 on November 18, 2014)
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30	Stanton, Robert et al., "Chemical Modification Study of Antisense Gapmers", Nucleic Acid Therapeutics, Vol. 22(5): 344-359 (2012)
31	Statement On A Nonproprietary Name Adopted By the USAN Council, ETEPLIRSEN, Chemical Structure, 2010, pages 1-5.
32	STEIN, CA, "Delivery of antisense oligonucleotides to cells: a consideration of some of the barriers," Monographic supplement series: Oligos & Peptides - Chimica Oggi - Chemistry Today, Vol. 32(2):4-7 (2014) (Exhibit Number 2022 filed in interferences 106008, 106013, 106007 on November 18, 2014)
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34	STEIN, David et al., "A Specificity Comparison of Four Antisense Types: Morpholino, 2'-O-Methyl RNA, DNA, and Phosphorothioate DNA," Antisense & Nucleic Acid Drug Development, Vol. 7:151-157 (1997)
35	Strober JB, "Therapeutics in Duchenne muscular dystrophy," NeuroRX 2006; 3:225-34.
36	Summary of Professional Experience (Dr. Erik J. Sontheimer), Pages 4, Exhibit Number 1223 filed in Interferences 106,007 and 106,008 on February 17, 2015.
37	SUMMERTON, James et al., "Morpholino and Phosphorothioate Antisense Oligomers Compared in Cell-Free and In-Cell Systems," Antisense & Nucleic Acid Drug Development, Vol. 7:63-70 (1997)
38	SUMMERTON, James et al., "Morpholino Antisense Oligomers: Design, Preparation, and Properties," Antisense & Nucleic Acid Drug Development, Vol. 7:187-195 (1997)
39	SUMMERTON, James, "Morpholino antisense oligomers: the case for an RNase H-independent structural type," Biochimica et Biophysica Acta, Vol. 1489:141-158 (1999) (Exhibit Number 1038 filed in interferences 106008, 106013, 106007 on November 18, 2014)
40	Supplementary European Search Report for Application No. 10829367.1, 8 pages, dated May 22, 2013
41	Suter et al., "Double-target antisense U7 snRNAs promote efficient skipping of an aberrant exon in three human Beta-thalassemic mutations," 8:13 HUMAN MOLECULAR GENETICS 2415-2423 (1999) (Exhibit Number 1083 filed in interferences 106008, 106007 on December 23, 2014)
42	T HOEN, Peter A.C. et al., "Generation and Characterization of Transgenic Mice with the Full-length Human DMD Gene," The Journal of Biological Chemistry, Vol. 283(9):5899-5907 (2008) Exhibit Number 2030 filed in interferences 106008, 106013, 106007 on November 18, 2014)
43	Table 1: Primer and Product Details for Exon 51 and 53 Reports on AONs of 20 to 50 Nucleotides dd 07 JAN 2015, Pages 1, Exhibit Number 1177 filed in Interferences 106,007 and 106,008 on February 16, 2015.
44	Takeshima et al., "Oligonucleotides against a splicing enhancer sequence led to dystrophin production in muscle cells from a Duchenne muscular dystrophy patient," Brain & Dev., Vol. 23, pp. 788-790 (2001), Exhibit Number 1196 filed in Interferences 106,007 and 106,008 on February 17, 2015.

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46	TANAKA, Kenji et al., "Polypurine Sequences within a Downstream Exon Function as a Splicing Enhancer," Molecular and Cellular Biology, Vol. 14(2):1347-1354 (1994)
47	Telios Pharms., Inc. v. Merck KgaA, No. 96-1307, 1998 WL 35272018 (S.D. Cal. Nov. 18, 1998), 11 pages (Exhibit Number 2153 filed in interference 106013 on October 29, 2015)
48	THANH, Le Htiet et al., "Characterization of Revertant Muscle Fibers in Duchenne Muscular Dystrophy, Using Exon-Specific Monoclonal Antibodies against Dystrophin," Am. J. Hum. Genet., Vol. 56:725-731 (1995)
49	The Regents of the University of California v. Dako North America, Inc., U.S.D.C., N.D. California, No. C05-03955 MHP, April 22, 2009 (2009 WL 1083446 (N.D.Cal.), Exhibit Number 1206 filed in Interferences 106,007 and 106,008 on February 17, 2015.
50	TIAN, Xiaobing et al., "Imaging Oncogene Expression," Ann. N.Y. Acad. Sci., Vol. 1002:165-188 (2003) (Exhibit Number 2029 filed in interferences 106008, 106013, 106007 on November 18, 2014)

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☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

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SIGNATURE

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Signature	/Amy E. Mandragouras, Esq./	Date (YYYY-MM-DD)	2017-09-22
Name/Print	Amy E. Mandragouras, Esq.	Registration Number	36,207

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/KIMBERLY CHONG/ (10/01/2017)

10/01/2017

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	Filing Date	2017-09-14
	First Named Inventor	Stephen Donald WILTON
	Art Unit	1674
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AVN-008CN41

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1	Excerpts of SEC Form 8-K, dated November 23 2014, for BioMarin Pharmaceutical Inc., (University of Western Australia Exhibit 2129, filed April 3, 2015 in Interferences 106007, 106008, and 106013, pages 1-9).
2	Exon 46 Sequence of Dystrophin, Document D18 as filed in Opposition of European Patent EP1619249, filed June 23, 2009, 1 page
3	Exon 51 Internal Sequence Schematic, Pages 1, Exhibit Number 1224 filed in Interferences 106,007 and 106,008 on February 17, 2015.
4	Exon 53 Internal Sequence Schematic, Pages 1, Exhibit Number 1225 filed in Interferences 106,007 and 106,008 on February 17, 2015.
5	Extended European Search Report, EP 15190341.6, dated April 28, 2016, 9 pages.
6	Fairclough et al., "Therapy for Duchenne muscular dystrophy: renewed optimism from genetic approaches," Nature Reviews, Vol. 14, pp. 373-378 (June, 2013), Exhibit Number 1112 filed in interferences 106,007 and 106,008 on February 17, 2015.
7	FALL, Abbie M. et al., "Induction of revertant fibres in the mdx mouse using antisense oligonucleotides," Genetics Vaccines and Therapy, Vol. 4:3, doi:10.1186/1479-0556-4-3, 12 pages (2006)
8	FDA Briefing Document, "Peripheral and Central Nervous System," Drugs Advisory Committee Meeting, NDA 206488 Eteplirsen, Food and Drug Administration, pages 1-73, January 22, 2016.
9	FDA Briefing Information for the April 25, 2016 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, Eteplirsen, NDA 206488, 115 pages
10	FDA News Release, "FDA grants accelerated approval to first drug for Duchenne muscular dystrophy," September 19, 2016, 3 pages.
11	Federal Register, Vol. 58, No. 183, pp. 49432-49434, September 23, 1993 (6 pages); [Cited as: 58 FR 49432-01, 1993 WL 371451 (F.R.)], Exhibit Number 1221 filed in Interferences 106,007 and 106,008 on February 17, 2015.

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12	Federal Register, Vol. 69, No. 155, pp. 49960-50020 dated August 12, 2004 (62 pages), Exhibit Number 1220 filed in Interferences 106,007 and 106,008 on February 17, 2015.
13	FEENER, C. et al., "Alternative splicing of human dystrophin mRNA generates isoforms at the carboxy terminus," Nature, vol. 338:509 - 511 (1989).
14	File Excerpt from AZL U.S. Patent Application 11/233,495: Amendment After Non-Final Office Action, as-filed November 1, 2010 (Exhibit Number 1085 filed in interferences 106008, 106007 on December 23, 2014)
15	File Excerpt from AZL U.S. Patent Application 11/233,495: Claims examined in Non-Final Office Action, dated December 1, 2008 (Exhibit Number 1079 filed in interferences 106008, 106007 on December 23, 2014)
16	File Excerpt from AZL U.S. Patent Application 11/233,495: Final Office Action dated August 31, 2010 (Exhibit Number 1086 filed in interferences 106008, 106007 on December 23, 2014)
17	File Excerpt from U.S. Patent Application 11/233,495: Non-Final Office Action dated December 1, 2008 and Final Office Action dated June 25, 2009 (Exhibit Number 1078 filed in interferences 106008, 106007 on December 23, 2014)
18	File Excerpt from U.S. Patent Application No. 12/198,007: AZL's Preliminary Amendment and Response, as-filed November 7, 2008 (Exhibit Number 1075 filed in interferences 106008, 106007 on December 23, 2014)
19	File Excerpt from U.S. Patent Application No. 12/976,381: AZL's First Preliminary Amendment, as-filed December 22, 2010 (Exhibit Number 1076 filed in interferences 106008, 106007 on December 23, 2014)
20	File Excerpts from Prosecution History of U.S. Patent Application No. 13/270,992 ("UWA's U.S. Patent 8,486,907"), Pages 122, Exhibit Number 1006 filed in Interference 106,013 on February 17, 2015.
21	File Excerpts from U.S. Patent Application No. 11/233,495: Response to Non- Final Office Action, as filed July 26, 2011 (14 pages), Exhibit Number 1222 filed in Interferences 106,007 and 106,008 on February 17, 2015.
22	File Excerpts from U.S. Patent Application No. 13/270,992 ("UWA's U.S. Patent 8,486,907"): NFOA, dated 7/30/2012; Applicant-Initiated Interview Summary, dated 11/8/2012; Amendment, as filed January 30, 2013; NOA, dated 4/4/2013, Exhibit Number 1118 (122 pages) filed in interferences 106,007 and 106,008 on February 17, 2015.

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23	Flanagan, W. Michael, et al., "A cytosine analog that confers enhanced potency to antisense oligonucleotides," Proc. Nat'l Acad. Sci. USA, Vol. 96, pp. 3513-3518 (March, 1999), Exhibit Number 1211 filed in Interferences 106,007 and 106,008 on February 17, 2015.
24	Flanigan et al. (2003) "Rapid Direct Sequence Analysis of the Dystrophin Gene," Am. J. Hum. Genet. 72:931-939, dated February 17, 2015 (Exhibit Number 2120 filed in interferences 106,007 and 106,008 on February 17, 2015.
25	FLANIGAN, Kevin M. et al., "Pharmacokinetics and safety of single doses of drisapersen in non-ambulant subjects with Duchenne muscular dystrophy: Results of a double-blind randomized clinical trial," Neuromuscular Disorders, Vol. 24:16-24 (2014) (Exhibit Number 2038 filed in interferences 106008, 106013, 106007 on November 18, 2014)
26	Fletcher S., et al, "Morpholino oligomer-mediated exon skipping averts the onset of dystrophic pathology in the mdx mouse. Mol Ther 2007;15:1587-1592.
27	FLETCHER, Sue et al., "Dystrophin Isoform Induction In Vivo by Antisense-mediated Alternative Splicing," Molecular Therapy, Vol. 18(6):1218-1223 (2010)
28	FLETCHER, Sue et al., "Targeted Exon Skipping to Address 'Leaky' Mutations in the Dystrophin Gene," Molecular Therapy-Nucleic Acids, Vol. 1, e48, doi:10.1038/mtna.2012.40, 11 pages (2012)
29	FLETCHER, Susan et al., "Dystrophin expression in the mdx mouse after localised and systemic administration of a morpholino antisense oligonucleotide," J. Gene Med., Vol. 8:207-216 (2006)
30	FLETCHER, Susan et al., "Gene therapy and molecular approaches to the treatment of hereditary muscular disorders," Curr. Opin. Neurol., Vol. 13:553-560 (2000)
31	FOSTER, Helen et al., "Genetic Therapeutic Approaches for Duchenne Muscular Dystrophy," Human Gene Therapy, Vol. 23:676-687 (2012)
32	Fourth Declaration of Erik Sontheimer, Ph.D. (Pursuant to Bd.R. 41.155(b)(2) and SO 155.1.3 and 155.1.4), dated March 9, 2015, (University of Western Australia Exhibit 2138, filed April 3, 2015 in Interferences 106007, 106008, and 106013, pages 1-4).
33	FRAGALL, Clayton T. et al., "Mismatched single stranded antisense oligonucleotides can induce efficient dystrophin splice switching," BMC Medical Genetics, Vol. 12:141, 8 pages (2011) (Exhibit Number 2019 filed in interferences 106008, 106013, 106007 on November 18, 2014)

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34	FRALEY, Robert et al., "New generation of liposomes: the engineering of an efficient vehicle for intracellular delivery of nucleic acids," Trends Biochem., Vol. 6:77-80 (1981)
35	FRAZIER, Kendall S. et al., "Species-specific Inflammatory Responses as a Primary Component for the Development of Glomerular Lesions in Mice and Monkeys Following Chronic Administration of a Second-generation Antisense Oligonucleotide," Toxicologica Pathology, 13 pages (2013)
36	FRIEDMANN, Theodore, "Progress Toward Human Gene Therapy," Science, Vol. 244(4910):1275-1281 (1989)
37	GEBSKI, Bianca L. et al., "Morpholino antisense oligonucleotide induced dystrophin exon 23 skipping in mdx mouse muscle," Human Molecular Genetics, Vol. 12(15):1801-1811 (2003)
38	GenBank AF213437.1 Dated January 17, 2002
39	Generic Method for Average Mass Determination Using LC-UV-MS in the Negative Mode, Pages 15, Exhibit Number 1145 filed in Interferences 106,007 and 106,008 on February 16, 2015.
40	Generic UPLC Purity Method for Oligonucleotides (19- to 25-mers), Pages 18, Exhibit Number 1156 filed in Interferences 106,007 and 106,008 on February 16, 2015.
41	GENNARO, Alfonso R., (ed.), Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing, Co., Easton PA, 2020 pages (1990)
42	GILES, Richard V. et al., "Antisense Morpholino Oligonucleotide Analog Induces Missplicing of C-myc mRNA," Antisense & Nucleic Acid Drug Development, Vol. 9:213-220 (1999)
43	GlaxoSmithKline Press Release, Issued in London, UK, dated June 27, 2013 (5 pages), Exhibit Number 1202 filed in Interferences 106,007 and 106,008 on February 17, 2015.
44	GlaxoSmithKline, "GSK and Prosensa announce start of Phase III study of investigational Duchenne Muscular Dystrophy medication," press release, 6 pages, dated January 19, 2011 (Exhibit Number 2060 filed in interferences 106008, 106013, 106007 on November 18, 2014)

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45	GlaxoSmithKline, "Prosensa regains rights to drisapersen from GSK and retains rights to all other programmes for the treatment of Duchenne muscular dystrophy (DMD), press release, 4 pages, dated January 13, 2014 (Exhibit 2040 in Interferences 106007, 106008, and 106013 on November 18, 2014).
46	GOEMANS, Nathalie M. et al., "Systemic Administration of PRO051 in Duchenne's Muscular Dystrophy," The New England Journal of Medicine, Vol. 364:1513-1522 (2011) (Exhibit Number 2036 filed in interferences 106008, 106013, 106007 on November 18, 2014)
47	Gordon et al., "Kinetic Characterization of the Second Step of Group II Intron Splicing: Role of Metal Ions and the Cleavage Site 2'-OH in Catalysis," Biochemistry, Vol. 39, pp. 12939-12952 (2000), Exhibit Number 1188 filed in Interferences 106,007 and 106,008 on February 17, 2015.
48	GORDON, Peter M. et al., "Metal ion catalysis during the exon-ligation step of nuclear pre-mRNA splicing: Extending the parallels between the spliceosome and group II introns," RNA, Vol. 6:199-205 (2000) (Exhibit Number 1055 filed in interferences 106008, 106007 on November 18, 2014)
49	GOYENVALLE, Aurelie et al., "Prevention of Dystrophic Pathology in Severely Affected Dystrophin/Utrophin-deficient Mice by Morpholino-oligomer-mediated Exon-skipping," Molecular Therapy, Vol. 18(1):198-205 (2010)
50	HAMMOND, Suzan M. et al., "Correlating In Vitro Splice Switching Activity With Systemic In Vivo Delivery Using Novel ZEN-modified Oligonucleotides," Molecular Therapy - Nucleic Acids, Vol. 3:1, 11 pages (2014) (Exhibit Number 2011 filed in interferences 106008, 106013, 106007 on November 18, 2014)

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Examiner Signature	/KIMBERLY CHONG/ (10/01/2017)	Date Considered	10/01/2017
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1	MITRPANT, Chalermchai et al., "Rational Design of Antisense Oligomers to Induce Dystrophin Exon Skipping," Molecular Therapy, Vol. 17(8):1418-1426 (2009)
2	MONACO, Anthony P. et al., "An Explanation for the Phenotypic Differences between Patients Bearing Partial Deletions of the DMD Locus," Genomics, Vol. 2:90-95 (1988)
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	1	2011/045747	WO	A1	2011-04-21	Universita Delgi Studi Di Ferrara		
	2	2011/057350	WO	A1	2011-05-19	The University of Western Australia		
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4	2012/001941	WO	A1	2012-01-05	Hagiwara, Masatoshi et al.	×
5	2012/029986	WO	A1	2012-03-08	Nippon Shinyaku Co., Ltd. et al.	<input type="checkbox"/>
6	2012/043730	WO	A1	2012-04-05	Nippon Shinyaku Co., Ltd.	<input checked="" type="checkbox"/>
7	2012/109296	WO	A1	2012-08-16	The Charlotte-Mecklenburg Hospital Authority D/B/A	<input type="checkbox"/>
8	2012/150960	WO	A1	2012-11-08	Avi Biopharma, Inc	<input type="checkbox"/>
9	2013/033407	WO	A2	2013-03-07	The Regents of the University of California	<input type="checkbox"/>
10	2013/053928	WO	A1	2013-04-18	Association Institut De Myologie et al.	<input type="checkbox"/>
11	2013/100190	WO	A1	2013-07-04	Nippon Shinyaku Co., Ltd. et al.	<input checked="" type="checkbox"/>
12	2013/112053	WO	A1	2013-08-01	Prosensa Technologies B.V.	<input type="checkbox"/>
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20	2017/059131	WO	A1	2017-04-06	Sarepta Therapeutics, Inc	<input type="checkbox"/>
21	93/20227	WO	A1	1993-10-14	Abbott Laboratories	<input type="checkbox"/>
22	94/02595	WO	A1	1994-02-03	Ribozyme Pharmaceuticals, Inc.	<input type="checkbox"/>
23	94/26887	WO	A1	1994-11-24	The University of North Carolina at Chapel Hill	<input type="checkbox"/>
24	96/10391	WO	A1	1996-04-11	The University of British Columbia	<input type="checkbox"/>
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26	97/30067	WO	A1	1997-08-21	sis Pharmaceuticals, Inc.	<input type="checkbox"/>
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	1	Classification Excerpts from USPC System, 21 pages, (Academisch Ziekenhuis Leiden Exhibit 1234, filed May 5, 2015 in Interference 106007 and 106008).	
	2	COLLINS, C.A. et al., "Duchenne's muscular dystrophy: animal models used to investigate pathogenesis and develop therapeutic strategies," Int. J. Exp. Pathol., Vol. 84(4):165-172 (2003)	
	3	Confirmation of Dystrophin Exon 48 to 50 Deletion in Cell Line 8036 Laboratory Notebook Entry, Pages 3, Exhibit Number 1167 filed in Interferences 106,007 and 106,008 on February 16, 2015.	
	4	Confirmation of Dystrophin Exon 52 Deletion in Cell Line R1809 Laboratory; Notebook Entry, Pages 3, Exhibit Number 1168 filed in Interferences 106,007 and 106,008 on February 16, 2015.	
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8	Corrected Priority Statement filed by UWA in Int. No. 106,008 (as PN 219), Pages 5, Exhibit Number 1002 filed in Interference 106,013 on February 17, 2015.
9	Cortes et al., "Mutations in the conserved loop of human U5 snRNA generate use of novel cryptic 5' splice sites in vivo," EMBO J., Vol. 12, No. 13, pp. 5181-5189 (1993), Exhibit Number 1187 filed in Interferences 106,007 and 106,008 on February 17, 2015.
10	CROOKE, Stanley T., Antisense Drug Technology, Principles, Strategies, and Applications, Marcel Dekker, Inc., New York, Chapters 15 and 16, pages 375-389, 391-469 (2001) (Exhibit Number 2075 filed in interferences 106008, 106013, 106007 on November 18, 2014)
11	Curriculum Vitae of Judith van Deutekom, Pages 6, Exhibit Number 1126 filed in interferences 106,007 and 106,008 on February 17, 2015.
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14	DAVIS, Richard J. et al., "Fusion of PAX7 to FKHR by the Variant t(1;13)(p36;q14) Translocation in Alveolar Rhabdomyosarcoma," Cancer Research, Vol. 54:2869-2872 (1994) (Exhibit Number 1027 filed in interferences 106008, 106007 on November 18, 2014)
15	DE ANGELIS, Fernanda Gabriella et al., "Chimeric snRNA molecules carrying antisense sequences against the splice junctions of exon 51 of the dystrophic pre-mRNA induce exon skipping and restoration of a dystrophin synthesis in 48-50 DMD cells," PNAS, Vol. 99(14):9456-9461 (2002)
16	Decision on Appeal, Ex Parte Martin Gleave and Hideaki Miyake, Appeal No. 2005-2447, Appl. No. 09/619,908 (January 31, 2006) (2009 WL 6927761 (Bd.Pat.App.& Interf.)), Pages 12, Exhibit Number 1207 filed in Interferences 106,007 and 106,008 on February 17, 2015.
17	Decision on Request for ReHearing, Ex Parte Roderick John Scott, Appeal No. 2008-004077, Appl. No. 10/058,825 (January 6, 2010) (2010 WL 191079 (Bd.Pat.App. & Interf.)), Pages 21, Exhibit Number 1208 filed in Interferences 106,007 and 106,008 on February 17, 2015.
18	Declaration of Judith C.T. van Deutekom Under 37 C.F.R. §1.132, filed on January 27, 2012, in U.S. Patent Reexamination Control No 90/011,320, regarding U.S. Patent No. 7,534,879, (University of Western Australia Exhibit 2133, filed April 3, 2015 in Interferences 106007, 106008, and 106013, pages 1-10).

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Application Number	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

19	Declaration of Judith van Deutekom, Pages 45, Exhibit Number 1125 filed in interferences 106,007 and 106,008 on February 17, 2015.
20	DELLORUSSO, Christiana et al., "Functional correction of adult mdx mouse muscle using gutted adenoviral vectors expressing full-length dystrophin," PNAS, Vol. 99(20):12979-12984 (2002)
21	Deposition Transcript of Erik J. Sontheimer, Ph.D. of January 21, 2015 (99 pages), Exhibit Number 1215 filed in interferences 106,007 and 106,008 on February 17, 2015.
22	Deposition Transcript of Matthew J. A. Wood, M.D., D. Phil., January 22, 2015, including Errata Sheet, Pages 198, Exhibit Number 1007 filed in Interference 106,013 on February 17, 2015.
23	Deposition Transcript of Matthew J. A. Wood, M.D., D. Phil., Pages 196, Exhibit Number 1122 filed in interferences 106,007 and 106,008 on February 17, 2015.
24	Desalting of Oligonucleotides, Pages 2, Exhibit Number 1132 filed in Interferences 106,007 and 106,008 on February 17, 2015.
25	DIRKSEN, Wessel P. et al., "Mapping the SF2/ASF Binding Sites in the Bovine Growth Hormone Exonic Splicing Enhancer," The Journal of Biological Chemistry, Vol. 275(37):29170-29177 (2000)
26	DOMINSKI, Zbigniew et al., "Identification and Characterization by Antisense Oligonucleotides of Exon and Intron Sequences Required for Splicing," Molecular and Cellular Biology, Vol. 14(11):7445-7454 (1994)
27	DOMINSKI, Zbigniew et al., "Restoration of correct splicing in thalassemic pre-mRNA by antisense oligonucleotides," Proc. Natl. Acad. Sci. USA, Vol. 90:8673-8677 (1993)
28	DORAN, Philip et al., "Proteomic profiling of antisense-induced exon skipping reveals reversal of pathobiochemical abnormalities in dystrophic mdx diaphragm," Proteomics, Vol. 9:671-685, DOI 10.1002/pmic.200800441 (2009)
29	DOUGLAS, Andrew G.L. et al., "Splicing therapy for neuromuscular disease," Molecular and Cellular Neuroscience, Vol. 56:169-185 (2013) (Exhibit Number 2005 filed in interferences 106008, 106013, 106007 on November 18, 2014)

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30	Doyle, Donald F., et al. (2001) "Inhibition of Gene Expression Inside Cells by PeptideNucleic Acids: Effect of mRNA Target Sequence, Mismatched Bases, and PNA Length," Biochemistry 40:53-64, (Exhibit Number 2123 filed in Interferences 106,007 and 106,008 on February 17, 2015.
31	Dr. Wood Errata Sheet - 22 Jan 2015, Pages 2, Exhibit Number 1227 filed in Interferences 106,007 and 106,008 on February 17, 2015.
32	DUNCKLEY, Matthew G. et al., "Modification of splicing in the dystrophin gene in cultured Mdx muscle cells by antisense oligoribonucleotides," Human Molecular Genetics, Vol. 5(1):1083-1090 (1995)
33	DUNCKLEY, Matthew G. et al., "Modulation of Splicing in the DMD Gene by Antisense Oligoribonucleotides," Nucleosides & Nucleotides, Vol. 16(7-9):1665-1668 (1997)
34	ECKSTEIN, F., "Nucleoside Phosphorothioates," Ann. Rev. Biochem., Vol. 54:367-402 (1985) (Exhibit Number 1028 filed in interferences 106008, 106007 on November 18, 2014)
35	ELAYADI, Anissa N. et al., "Application of PNA and LNA oligomers to chemotherapy," Current Opinion in Investigational Drugs, Vol. 2(4):558-561 (2001)
36	Email from Danny Huntington to Interference Trial Section, dated September 21, 2014, Pages 2, Exhibit Number 3001 filed in Interference 106,007, 106,008, and 106,013 on September 26, 2014.
37	Email From Sharon Crane to Interference Trial Section, dated November 13, 2014, Pages 2, Exhibit Number 3002 filed in Interference 106,007, 106,008, and 106,013 on dated November 14, 2014.
38	Emery, A.E. H., "Population frequencies of inherited neuromuscular diseases - a world survey," Neuromuscul Disord 1991;1:19-29.
39	Errata sheet for the January 22, 2015 deposition of Matthew J. A. Wood, M.D., D. PHIL., 2 pages, (Exhibit Number 2128 filed in interferences 106,007 and 106,008 on February 17, 2015.
40	Errata sheet for the March 12, 2015 deposition of Erik J. Sontheimer, Ph.D., (University of Western Australia Exhibit 2149, filed April 3, 2015 in Interferences 106007, 106008, and 106013, page 1).

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41	Errata to the Sarepta Briefing Information for the April 25, 2016 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, Eteplirsen Errata Document, NDA 206488, 5 pages.
42	ERRINGTON, Stephen J. et al., "Target selection for antisense oligonucleotide induced exon skipping in the dystrophin gene," The Journal of Gene Medicine, Vol. 5:518-527 (2003)
43	European Office Action for Application No. 09752572.9, 5 pages, dated February 29, 2012
44	European Response, Application No. 10004274.6, 7 pages, dated November 5, 2013 (Exhibit Number 1060 filed in interferences 106008, 106007 on November 18, 2014)
45	European Response, Application No. 12198517.0, 7 pages, dated October 21, 2014 (Exhibit Number 2084 filed in interferences 106008, 106013, 106007 on November 18, 2014)
46	European Search Report for Application No. 10004274.6, 12 pages, dated January 2, 2013
47	European Search Report, EP15168694.6, dated July 23, 2015, pages 1-8.
48	Excerpts from Prosecution History of Application No. 13/741,150: Notice of Allowance dated March 16, 2015; List of References cited by Applicant and Considered by Examiner; Notice of Allowance and Fees due dated September 18, 2014; Amendment in Response to Non-Final Office Action dated July 11, 2014, (Academisch Ziekenhuis Leiden Exhibit 1229, filed April 3, 2015 in Interference 106007 and 106008, pages 1-133).
49	Excerpts from Prosecution History of Application No. 13/826,880: Notice of Allowance dated January 26, 2015 and Amendment in Response to Non-Final Office Action dated October 15, 2014, (Academisch Ziekenhuis Leiden Exhibit 1228, filed April 3, 2015 in Interference 106007 and 106008, pages 1-16).
50	Excerpts from Yeo (Ed.), "Systems Biology of RNA Binding Proteins," Adv. Exp. Med. Biol., Chapter 9, 56 pages (2014), (Academisch Ziekenhuis Leiden Exhibit 1232, filed April 3, 2015 in Interference 106007 and 106008, pages 1-56).

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Signature	/Amy E. Mandragouras, Esq./	Date (YYYY-MM-DD)	2017-09-22
Name/Print	Amy E. Mandragouras, Esq.	Registration Number	36,207

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1	Laboratory Notebook Entry (Exon 51 Experiments): RT-PCR Analysis of 8036 Cells, Pages 2, Exhibit Number 1179 filed in Interferences 106,007 and 106,008 on February 16, 2015.
2	Laboratory Notebook Entry (Exon 51 Experiments): RT-PCR Analysis of KM155.C25 Cells, Pages 2, Exhibit Number 1178 filed in Interferences 106,007 and 106,008 on February 16, 2015.
3	Laboratory Notebook Entry (Exon 51 Experiments): Transfection of 8036 Cells, Pages 1, Exhibit Number 1172 filed in Interferences 106,007 and 106,008 on February 16, 2015.
4	Laboratory Notebook Entry (Exon 51 Experiments): Transfection of KM155.C25 Cells, Pages 1, Exhibit Number 1171 filed in Interferences 106,007 and 106,008 on February 16, 2015.
5	Laboratory Notebook Entry (Exon 53 Experiments): RT-PCR Analysis of KM155.C25 Cells, Pages 2, Exhibit Number 1180 filed in Interferences 106,007 and 106,008 on February 16, 2015.
6	Laboratory Notebook Entry (Exon 53 Experiments): RT-PCR Analysis of R1809 Cells, Pages 2, Exhibit Number 1181 filed in Interferences 106,007 and 106,008 on February 16, 2015.
7	Laboratory Notebook Entry (Exon 53 Experiments): Transfection of KM155.C25 Cells, Pages 1, Exhibit Number 1173 filed in Interferences 106,007 and 106,008 on February 16, 2015.
8	Laboratory Notebook Entry (Exon 53 Experiments): Transfection of R1809 Cells, Pages 1, Exhibit Number 1174 filed in Interferences 106,007 and 106,008 on February 16, 2015.
9	Claims from US Application No. 11/233,495, 6 pages, dated September 21, 2005 (Exhibit Number 2068 filed in Interferences 106008, 106013, 106007 on November 18, 2014)
10	Laboratory Notebook Entry: General RNA recovery, Pages 2, Exhibit Number 1176 filed in Interferences 106,007 and 106,008 on February 16, 2015.
11	Laboratory Notebook Entry: Lab-on-a-Chip Analysis, Pages 3, Exhibit Number 1184 filed in Interferences 106,007 and 106,008 on February 16, 2015.

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12	Larsen et al., "Antisense properties of peptide nucleic acid," Biochim. Et Biophys. Acta, Vol. 1489, pp. 159-166 (1999), Exhibit Number 1190 filed in Interferences 106,007 and 106,008 on February 17, 2015.
13	Letter from the FDA to Sarepta Therapeutics, Inc., Re: ACCELERATED APPROVAL for the use of Exondys 51 (eteplirsen), FDA Reference ID: 3987286, dated September 19, 2016, 11 pages.
14	Letter to the U.S. Food and Drug Administration, (Dr. Billy Dunn, M.D. Director Division of Neurology Products, Office of Drug Evaluation 1, Center for Drug Evaluation and Research), for The Peripheral and Central Nervous System Advisory Committee Meeting (AdComm) supporting approval of eteplirsen, dated February 24, 2016, 4 pages.
15	Letter to the U.S. Food and Drug Administration, (Dr. Janet Woodcock, M.D. Director, CDER), from The Congress of The United States regarding Duchenne muscular dystrophy, dated February 17, 2016, 7 pages.
16	List of Publications for Matthew J. A. Wood, M.D., D. PHIL., 11 pages, (Exhibit Number 2124 filed in interferences 106,007 and 106,008 on February 17, 2015).
17	LIU, Hong-Xiang et al., "Identification of functional exonic splicing enhancer motifs recognized by individual SR proteins," Genes & Development, Vol. 12:1998-2012 (1998)
18	Lu et al, "Massive Idiosyncratic Exon Skipping Corrects the Nonsense Mutation in Dystrophic Mouse Muscle and Produces Functional Revertant Fibers by Clonal Expansion," THE JOURNAL OF CELL BIOLOGY, Vol. 148(5): 985-995, March 6, 2000 ("Lu et al.") (Exhibit Number 1082 filed in interferences 106008, 106007 on December 23, 2014)
19	LU, Qi Long et al., "Functional amounts of dystrophin produced by skipping the mutated exon in the mdx dystrophic mouse," Nature Medicine, Vol. 9(8):1009-1014 (2003)
20	LU, Qi-long et al., "What Can We Learn From Clinical Trials of Exon Skipping for DMD?" Molecular Therapy - Nucleic Acids, Vol. 3:e152, doi:10.1038/mtna.2014.6, 4 pages (2014)
21	Lyophilisation of Oligonucleotides, Pages 2, Exhibit Number 1133 filed in Interferences 106,007 and 106,008 on February 17, 2015.
22	MANN, Christopher J. et al., "Antisense-induced exon skipping and synthesis of dystrophin in the mdx mouse," PNAS, Vol. 98(1):42-47 (2001)

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23	MANN, Christopher J. et al., "Improved antisense oligonucleotide induced exon skipping in the mdx mouse model of muscular dystrophy," The Journal of Gene Medicine, Vol. 4:644-654 (2002)
24	MANNINO, Raphael J. et al., "Liposome Mediated Gene Transfer," BioTechniques, Vol. 6(7):682-690 (1988)
25	Manual of Patent Examining Procedure 2308.02 (6th ed., rev. 3, July 1997), (University of Western Australia Exhibit 2143, filed April 3, 2015 in Interferences 106007, 106008, and 106013, pages 1-2).
26	Manzur A, et al., "Glucocorticoid corticosteroids for Duchenne muscular dystrophy," Cochrane Database Syst Rev. 2004;(2):CD003725.
27	MARSHALL, N.B. et al., "Arginine-rich cell-penetrating peptides facilitate delivery of antisense oligomers into murine leukocytes and alter pre-mRNA splicing," Journal of Immunological Methods, Vol. 325:114-126 (2007)
28	Mathews et al., "Expanded Sequence Dependence of Thermodynamic Parameters Improves Prediction of RNA Secondary Structure," J. Mol. Biol. 288:911-940 (1999), (University of Western Australia Exhibit 2131, filed April 3, 2015 in Interferences 106007, 106008, and 106013, pages 1-31).
29	Mathews et al., "Expanded Sequence Dependence of Thermodynamic Parameters Improves Prediction of RNA Secondary Structure," J. Mol. Biol., Vol. 288, pp. 911-940 (1999), Exhibit Number 1212 filed in Interferences 106,007 and 106,008 on February 17, 2015.
30	MATSUO, Masafumi et al., "Exon Skipping during Splicing of Dystrophin mRNA Precursor due to an Intraexon Deletion in the Dystrophin Gene of Duchenne Muscular Dystrophy Kobe," J. Clin. Invest., Vol. 87:2127-2131 (1991)
31	MATSUO, Masafumi et al., "Treatment of Duchenne Muscular Dystrophy with Oligonucleotides against an Exonic Splicing Enhancer Sequence," Basic Appl. Myol., Vol. 13(6):281-285 (2003)
32	MATSUO, Masafumi, "Duchenne and Becker Muscular Dystrophy: From Gene Diagnosis to Molecular Therapy," JUBMB Life, Vol. 53:147-152 (2002)
33	MATSUO, Masafumi, "Duchenne/Becker muscular dystrophy: from molecular diagnosis to gene therapy," Brain & Development, Vol. 18:167-172 (1996)

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34	MATTEUCCI, Mark, "Structural modifications toward improved antisense oligonucleotides," Perspectives in Drug Discovery and Design, Vol. 4:1-16 (1996)
35	Mazzone E, et al. "Functional changes in Duchenne muscular dystrophy: a 12-month longitudinal cohort study," Neurology 2011;77(3):250-6.
36	MCCARVILLE, M. Beth et al., "Rhabdomyosarcoma in Pediatric Patients: The Good, the Bad, and the Unusual," AJR, Vol. 176:1563-1569 (2001) (Exhibit Number 1034 filed in interferences 106008, 106007 on November 18, 2014)
37	MCCLOREY, G. et al., "Antisense oligonucleotide-induced exon skipping restores dystrophin expression in vitro in a canine model of DMD," Gene Therapy, Vol. 13:1373-1381 (2006)
38	MCCLOREY, G. et al., "Induced dystrophin exon skipping in human muscle explants," Neuromuscular Disorders, Vol. 16:583-590 (2006)
39	MCCLOREY, Graham et al., "Splicing intervention for Duchenne muscular dystrophy," Current Opinion in Pharmacology, Vol. 5:529-534 (2005)
40	McDonald CM, et al., "Profiles of Neuromuscular Diseases, Duchenne muscular dystrophy," Am J Phys Med Rehabil 1995;74:S70-S92
41	McDonald CM, et al., "The 6-minute walk test as a new outcome measure in Duchenne muscular dystrophy," Muscle Nerve 2010;41:500-10.
42	McDonald CM, et al., "The 6-minute walk test in Duchenne/Becker muscular dystrophy: longitudinal observations," Muscle Nerve 2010;42: 966-74.
43	Mendell JR et al., "Evidence-based path to newborn screening for Duchenne muscular Dystrophy," Ann Neurol 2012;71:304-13.
44	Mendell JR, et al., "Dystrophin immunity revealed by gene therapy in Duchenne muscular dystrophy," N Engl J Med 2010;363:1429-37.

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45	Mendell JR, et al., "Randomized, double-blind six-month trial of prednisone in Duchenne's muscular dystrophy," N Engl J Med 1989;320:1592-97.
46	MENDELL, Jerry R. et al., "Eteplirsen for the Treatment of Duchenne Muscular Dystrophy," Ann. Neurol., Vol. 74:637-647 (2013) (Exhibit Number 2058 filed in interferences 106008, 106013, 106007 on November 18, 2014)
47	MENDELL, Jerry R. et al., "Eteplirsen in Duchenne Muscular Dystrophy (DMD): 144 Week Update on Six-Minute Walk Test (6MWT) and Safety," slideshow, presented at the 19th International Congress of the World Muscle Society, 17 pages (2014) (Exhibit Number 2059 filed in interferences 106008, 106013, 106007 on November 18, 2014)
48	MENDELL, Jerry R. et al., "Gene therapy for muscular dystrophy: Lessons learned and path forward," Neuroscience Letters, Vol. 527:90-99 (2012)
49	Merlini L, et al., "Early corticosteroid treatment in 4 Duchenne muscular dystrophy patients: 14-year follow-up," Muscle Nerve 2012;45:796-802.
50	Mfold illustrations for Exon 51 and Exon 53 with varying amounts of intron sequence, (University of Western Australia Exhibit 2132, filed April 3, 2015 in Interferences 106007, 106008, and 106013, pages 1-2).

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SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Amy E. Mandragouras, Esq./	Date (YYYY-MM-DD)	2017-09-22
Name/Print	Amy E. Mandragouras, Esq.	Registration Number	36,207

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

/KIMBERLY CHONG/ (10/01/2017)

10/01/2017

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc code: IDS

36893

PTO/SB/08a (03-15)

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	15705172
	Filing Date	2017-09-14
	First Named Inventor	Stephen Donald WILTON
	Art Unit	1674
	Examiner Name	K. Chong
	Attorney Docket Number	AVN-008CN41

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	1	20170009234	A1	2017-01-12	WILTON et al.	

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Examiner Name	K. Chong
Attorney Docket Number	AVN-008CN41

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

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Signature	/Amy E. Mandragouras, Esq./	Date (YYYY-MM-DD)	2017-09-26
Name/Print	Amy E. Mandragouras, Esq.	Registration Number	36,207

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Doc code: IDS

36897

PTO/SB/08a (03-15)

Doc description: Information Disclosure Statement (IDS) Filed

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	Filing Date	2017-09-14
	First Named Inventor	Stephen Donald WILTON
	Art Unit	1674
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AVN-008CN41

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**INFORMATION DISCLOSURE
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Application Number	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
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Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

1	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Exhibit List as of November 18, 2014, 7 pages, Patent Interference No. 106,008, dated November 18, 2014 (Doc 216)
2	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Exhibit list, 7 pages, Patent Interference No. 106,007, dated November 18, 2014 (Doc 213)
3	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Exhibit list, 7 pages, Patent Interference No. 106,013, dated November 18, 2014 (Doc 134)
4	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Exhibit List, 7 pages, Patent Interference Nos. 106,008, dated December 12, 2014 (Doc 221)
5	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Exhibit List, 8 pages, Patent Interference No. 106,007, dated December 12, 2014 (Doc 217)
6	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA List of Proposed Motions, Patent Interference No. 106,007, 7 pages, dated September 10, 2014 (Doc 17)
7	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA List of Proposed Motions, Patent Interference No. 106,008, 6 pages, dated September 10, 2014 (Doc 16)
8	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Miscellaneous Motion 1 (for authorization to file terminal disclaimer), 5 pages, Patent Interference No. 106,008, dated October 17, 2014 (Doc 22)
9	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Motion 1 (For Judgment Under 35 U.S.C., section 112(a)), 40 pages, Patent Interference No. 106,007, dated November 18, 2014 (Doc 210)
10	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Motion 1 (For Judgment Under 35 § 112(a)) Patent Interference No. 106,008 (Doc 213), 38 Pages, on November 18, 2014
11	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Motion 1 (To Maintain Interference between UWA US Patent No. 8,486,907 and AZL USSN 14/198,992), 45 pages, Patent Interference No. 106,013, dated November 18, 2014 (Doc 133)

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12	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Motion 2 (For Judgment Under 35 U.S.C. section 112(b)), 32 pages, Patent Interference No. 106,008, dated November 18, 2014 (Doc 214)
13	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Motion 2 (For Judgment Under 35 U.S.C. section 112(b)), 34 pages, Patent Interference No. 106,007, dated November 18, 2014 (Doc 211)
14	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Motion 3 (For judgment that Claims 11-12, 14-15, and 17-29 of Application No. 13/550,210 are barred under 35 U.S.C. section 135(b)), 25 Pages, Patent Interference No. 106,008, dated November 18, 2014 (Doc 215)
15	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Filing Priority Statement, 2 pages, Patent Interference No. 106,008, dated November 18, 2014 (Doc 218)
16	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Recent Authority, filed in Patent Interference No. 106,007, July 2, 2015, pages 1-16 (Doc 469).
17	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Recent Authority, filed in Patent Interference No. 106,007, September 2, 2015, pages 1-18 (Doc 470).
18	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Recent Authority, filed in Patent Interference No. 106,008, July 2, 2015, pages 1-16 (Doc 477)
19	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Recent Authority, filed in Patent Interference No. 106,008, September 2, 2015, pages 1-18 (Doc 478).
20	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Related Proceedings, Patent Interference No. 106,007, 3 pages, dated August 1, 2014 (Doc 11)
21	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Related Proceedings, Patent Interference No. 106,008, 5 pages, dated August 7, 2014 (Doc 11)
22	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Related Proceedings, Patent Interference No. 106,013, 3 pages, dated October 14, 2014 (Doc 6)

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Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

23	US 7,960,541 (Wilton et al.), Pages 84, Exhibit Number 1002 filed in interferences 106,007 and 106,008 on November 18, 2014.
24	US 8,450,474 (Wilton et al.), Pages 95, Exhibit Number 1087 filed in interferences 106,007 and 106,008 on February 13, 2015.
25	US 8,455,634 (Wilton et al.) Pages 95, Exhibit Number 1088 filed in interferences 106,007 and 106,008 on February 13, 2015.
26	US 8,455,635 (Wilton et al.), Pages 96, Exhibit Number 1089 filed in interferences 106,007 and 106,008 on February 13, 2015.
27	US 8,455,636 (Wilton et al.), Pages 92, Exhibit Number 1003 filed in interferences 106,007 and 106,008 on November 18, 2014.
28	US 8,476,423 (Wilton et al.), Pages 95, Exhibit Number 1111 filed in interferences 106,007 and 106,008 on February 13, 2015.
29	US 8,501,703 (Bennett et al.), Pages 16, Exhibit Number 1090 filed in interferences 106,007 and 106,008 on February 13, 2015.
30	US 8,501,704 (Mourich et al.), Pages 39, Exhibit Number 1091 filed in interferences 106,007 and 106,008 on February 13, 2015.
31	US 8,524,676 (Stein et al.), Pages 28, Exhibit Number 1092 filed in interferences 106,007 and 106,008 on February 13, 2015.
32	US 8,524,880 (Wilton et al.), Pages 89, Exhibit Number 1093 filed in interferences 106,007 and 106,008 on February 13, 2015.
33	US 8,536,147 (Weller et al.), Pages 95, Exhibit Number 1094 filed in interferences 106,007 and 106,008 on February 17, 2015, Doc 251.

**INFORMATION DISCLOSURE
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Attorney Docket Number	AVN-008CN41

34	US 8,592,386 (Mourich et al.), Pages 46, Exhibit Number 1095 filed in interferences 106,007 and 106,008 on February 13, 2015.
35	US 8,618,270 (Iversen et al.), Pages 28, Exhibit Number 1096 filed in interferences 106,007 and 106,008 on February 13, 2015.
36	US 8,637,483 (Wilton et al.), Pages 157, Exhibit Number 1097 filed in interferences 106,007 and 106,008 on February 13, 2015.
37	US 8,697,858 (Iversen), Pages 95, Exhibit Number 1098 filed in interferences 106,007 and 106,008 on February 13, 2015.
38	US 8,703,735 (Iversen et al.) Pages 73, Exhibit Number 1099 filed in interferences 106,007 and 106,008 on February 13, 2015.
39	US 8,741,863 (Moulton et al.), Pages 68, Exhibit Number 1100 filed in interferences 106,007 and 106,008 on February 13, 2015.
40	US 8,759,307 (Stein et al.), Pages 35, Exhibit Number 1101 filed in interferences 106,007 and 106,008 on February 13, 2015.
41	US 8,779,128 (Hanson et al.), Pages 104, Exhibit Number 1102 filed in interferences 106,007 and 106,008 on February 13, 2015.
42	US 8,785,407 (Stein et al.), Pages 35, Exhibit Number 1103 filed in interferences 106,007 and 106,008 on February 13, 2015.
43	US 8,785,410 (Iversen et al.), Pages 20, Exhibit Number 1104 filed in interferences 106,007 and 106,008 on February 13, 2015.
44	US 8,835,402 (Kole et al.), Pages 27, Exhibit Number 1105 filed in interferences 106,007 and 106,008 on February 13, 2015.

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45	US 8,865,883 (Sazani et al.), Pages 199, Exhibit Number 1106 filed in interferences 106,007 and 106,008 on February 13, 2015.
46	US 8,871,918 (Sazani et al.), Pages 195, Exhibit Number 1107 filed in interferences 106,007 and 106,008 on February 13, 2015.
47	US 8,877,725 (Iversen et al.), Pages 34, Exhibit Number 1108 filed in interferences 106,007 and 106,008 on February 13, 2015.
48	US 8,895,722 (Iversen et al.), Pages 29, Exhibit Number 1109 filed in interferences 106,007 and 106,008 on February 13, 2015.
49	US 8,906,872 (Iversen et al.), Pages 69, Exhibit Number 1110 filed in interferences 106,007 and 106,008 on February 13, 2015.
50	US Abandonment for Application No. 13/902,376, 1 page, dated June 12, 2014 (Exhibit Number 1047 filed in interferences 106008, 106007 on November 18, 2014)

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Examiner Signature	/KIMBERLY CHONG/ (10/01/2017)	Date Considered	10/01/2017
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This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: September 22, 2017
Electronic Signature for Amy E. Mandragouras, Esq.: /Amy E. Mandragouras, Esq./

Docket No.: AVN-008CN41
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Stephen Donald Wilton *et al.*

Application No.: 15/705,172

Confirmation No.: 2879

Filed: September 14, 2017

Art Unit: 1674

For: ANTISENSE OLIGONUCLEOTIDES FOR
INDUCING EXON SKIPPING AND
METHODS OF USE THEREOF

Examiner: Not Yet Assigned

INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In compliance with 37 C.F.R. § 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the documents listed on the attached PTO/SB/08. It is respectfully requested that the documents listed on the PTO/SB/08 be expressly considered by the Examiner during the prosecution of this application, and that the documents be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

For the Examiner's convenience in reviewing this continuation application, Applicant submits a consolidated PTO/SB/08, listing all references cited during the prosecution of the parent applications. The present application is a continuation of U.S. Application No. 15/274,772, filed September 23, 2016 (Atty. Docket No. AVN-008CN37). In accordance with 37 C.F.R. §1.98(d), copies of the references previously cited by or submitted to the Office in the parent applications are not enclosed, but will be provided upon request.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.C/

SRPT-VYDS-0004711

Application No.: 15/705,172 (Information Disclosure Statement)

Docket No.: AVN-008CN41

Applicant calls to the attention of the Examiner the following Applications and Office Actions issued therein:

Applications				
<i>Examiner's Initials</i>	<i>Serial No.</i>	<i>Filing Date</i>	<i>First Named Inventor</i>	<i>Docket No.</i>
	11/570,691	January 15, 2008	Stephen Donald Wilton	AVN-008
	12/837,356	July 15, 2010	Stephen Donald Wilton	AVN-008CN
	12/837,359	July 15, 2010	Stephen Donald Wilton	AVN-008CN2
	12/860,078	August 20, 2010	Stephen Donald Wilton	AVN-008CN3
	13/168,857	June 24, 2011	Stephen Donald Wilton	AVN-008CN4
	13/168,863	June 24, 2011	Stephen Donald Wilton	AVN-008CN5
	13/270,500	October 11, 2011	Stephen Donald Wilton	AVN-008CN6
	13/270,531	October 11, 2011	Stephen Donald Wilton	AVN-008CN7
	13/270,744	October 11, 2011	Stephen Donald Wilton	AVN-008CN8
	13/270,937	October 11, 2011	Stephen Donald Wilton	AVN-008CN9
	13/270,992	October 11, 2011	Stephen Donald Wilton	AVN-008CN10
	13/271,080	October 11, 2011	Stephen Donald Wilton	AVN-008CN11
	13/727,415	December 26, 2012	Stephen Donald Wilton	AVN-008CN12
	13/741,150	January 14, 2013	Stephen Donald Wilton	AVN-008CN13
	13/826,613	March 14, 2013	Stephen Donald Wilton	AVN-008CN14
	13/826,880	March 14, 2013	Stephen Donald Wilton	AVN-008CN15
	13/902,376	May 24, 2013	Stephen Donald Wilton	AVN-008CN17
	13/963,578	August 9, 2013	Stephen Donald Wilton	AVN-008CN18

Application No.: 15/705,172 (Information Disclosure Statement)

Docket No.: AVN-008CN41

	14/086,859	November 21, 2013	Stephen Donald Wilton	AVN-008CN19
	14/178,059	February 11, 2014	Stephen Donald Wilton	AVN-008CN20
	14/223,634	March 24, 2014	Stephen Donald Wilton	AVN-008CN22
	14/273,318	May 8, 2014	Stephen Donald Wilton	AVN-008CN23
	14/273,379	May 8, 2014	Stephen Donald Wilton	AVN-008CN24
	14/316,603	June 26, 2014	Stephen Donald Wilton	AVN-008CN25
	14/316,609	June 26, 2014	Stephen Donald Wilton	AVN-008CN26
	14/317,952	June 27, 2014	Stephen Donald Wilton	AVN-008CN27
	14/740,097	June 15, 2015	Stephen Donald Wilton	AVN-008CN28
	14/852,090	September 11, 2015	Stephen Donald Wilton	AVN-008CN29RCE
	14/852,149	September 11, 2015	Stephen Donald Wilton	AVN-008CN30
	14/857,555	September 17, 2015	Stephen Donald Wilton	AVN-008CN31
	14/857,561	September 17, 2015	Stephen Donald Wilton	AVN-008CN32RCE
	14/858,250	September 18, 2015	Stephen Donald Wilton	AVN-008CN33
	15/274,719	September 23, 2016	Stephen Donald Wilton	AVN-008CN36
	15/274,772	September 23, 2016	Stephen Donald Wilton	AVN-008CN37
	15/349,535	11-11-2016	Stephen Donald Wilton	AVN-008RE
	12/605,276	October 23, 2009	Peter SAZANI	AVN-009RCE
	13/829,545	March 14, 2013	Peter SAZANI	AVN-009CN
	13/830,253	March 14, 2013	Peter SAZANI	AVN-009CN2
	14/523,610	October 24, 2014	Peter SAZANI	AVN-009DV
	14/852,257	September 11, 2015	Peter SAZANI	AVN-009DVCN1RCE

Application No.: 15/705,172 (Information Disclosure Statement)

Docket No.: AVN-008CN41

	14/852,264	September 11, 2015	Peter SAZANI	AVN-009DVCN2
	14/857,569	September 17, 2015	Peter SAZANI	AVN-009DVCN3
	14/857,590	September 17, 2015	Peter SAZANI	AVN-009DVCN4
	14/858,416	September 18, 2015	Peter SAZANI	AVN-009DVCN5
	14/743,856	June 18, 2015	R.K. BESTWICK	AVN-10PCCN
	14/213,629	March 14, 2014	E.M. KAYE	AVN-012ARCE
	14/214,567	March 14, 2014	E.M. KAYE	AVN-012BRCE
	14/213,607	March 14, 2014	R.K. BESTWICK	AVN-013A
	14/214,480	March 14, 2014	R.K. BESTWICK	AVN-013BRCE
	14/942,629	November 16, 2015	R.K. BESTWICK	AVN-013ACN
	13/509,331	July 9, 2012	S.D. WILTON	AVN-015US
	14/108,137	December 16, 2013	S.D. WILTON	AVN-015USCN
	14/944,886	November 18, 2015	S.D. WILTON	AVN-015USCN2
	14/213,641	March 14, 2014	R.K. BESTWICK	AVN-017RCE
	14/776,533	September 14, 2015	R.K. BESTWICK	AVN-017CPUS

Office Actions (copies enclosed)			
<i>Examiner's Initials</i>	<i>Serial No.</i>	<i>Date Mailed from USPTO</i>	<i>Examiner</i>
	11/570,691	August 16, 2010	Kimberly Chong
	11/570,691	March 15, 2010	Kimberly Chong
	11/570,691	May 26, 2009	Kimberly Chong
	12/837,356	May 3, 2013	Kimberly Chong
	12/837,356	April 3, 2013	Kimberly Chong
	12/837,356	August 2, 2012	Kimberly Chong
	12/837,359	March 12, 2012	Kimberly Chong
	12/837,359	October 5, 2011	Kimberly Chong
	12/837,359	March 30, 2011	Kimberly Chong
	12/837,359	December 22, 2010	Kimberly Chong
	12/860,078	February 14, 2011	Kimberly Chong
	13/168,857	July 12, 2012	Kimberly Chong
	13/168,863	March 8, 2013	Kimberly Chong
	13/168,863	October 11, 2012	Kimberly Chong
	13/168,863	August 8, 2012	Kimberly Chong

Application No.: 15/705,172 (Information Disclosure Statement)

Docket No.: AVN-008CN41

	13/270,500	March 15, 2013	Kimberly Chong
	13/270,500	July 30, 2012	Kimberly Chong
	13/270,500	March 14, 2012	Kimberly Chong
	13/270,531	June 28, 2012	Kimberly Chong
	13/270,531	March 14, 2012	Kimberly Chong
	13/270,744	April 3, 2013	Kimberly Chong
	13/270,744	August 6, 2012	Kimberly Chong
	13/270,744	March 14, 2012	Kimberly Chong
	13/270,937	February 25, 2013	Kimberly Chong
	13/270,937	June 14, 2012	Kimberly Chong
	13/270,937	March 14, 2012	Kimberly Chong
	13/270,992	April 4, 2013	Kimberly Chong
	13/270,992	July 30, 2012	Kimberly Chong
	13/270,992	March 16, 2012	Kimberly Chong
	13/271,080	March 26, 2013	Kimberly Chong
	13/271,080	July 30, 2012	Kimberly Chong
	13/271,080	March 14, 2012	Kimberly Chong
	13/727,415	February 6, 2013	Kimberly Chong
	13/741,150	March 16, 2015	Kimberly Chong
	13/741,150	September 18, 2014	Kimberly Chong
	13/741,150	April 11, 2014	Kimberly Chong
	13/741,150	September 24, 2013	Kimberly Chong
	13/826,613	July 22, 2014	Kimberly Chong
	13/826,613	January 7, 2014	Kimberly Chong
	13/826,613	July 17, 2013	Kimberly Chong
	13/826,880	June 22, 2015	Kimberly Chong
	13/826,880	January 26, 2015	Kimberly Chong
	13/826,880	April 15, 2014	Kimberly Chong
	13/826,880	September 11, 2013	Kimberly Chong
	13/902,376	June 5, 2014	Kimberly Chong
	13/902,376	January 7, 2014	Kimberly Chong
	13/902,376	July 18, 2013	Kimberly Chong
	13/963,578	September 24, 2013	Kimberly Chong
	14/086,859	June 30, 2014	Kimberly Chong
	14/086,859	January 27, 2014	Kimberly Chong
	14/178,059	March 31, 2014	Kimberly Chong
	14/223,634	April 15, 2015	Kimberly Chong
	14/273,318	October 20, 2014	Kimberly Chong
	14/273,318	July 3, 2014	Kimberly Chong
	14/273,379	July 7, 2014	Kimberly Chong
	14/316,603	March 10, 2015	Kimberly Chong
	14/316,603	September 26, 2014	Kimberly Chong

Application No.: 15/705,172 (Information Disclosure Statement)

Docket No.: AVN-008CN41

	14/316,609	March 16, 2015	Kimberly Chong
	14/316,609	October 21, 2014	Kimberly Chong
	14/317,952	March 18, 2015	Kimberly Chong
	14/317,952	November 7, 2014	Kimberly Chong
	14/740,097	November 14, 2016	Kimberly Chong
	14/740,097	April 8, 2016	Kimberly Chong
	14/740,097	November 6, 2015	Kimberly Chong
	14/852,090	April 15, 2016	Kimberly Chong
	14/852,090	January 6, 2016	Kimberly Chong
	14/852,090	October 15, 2015	Kimberly Chong
	14/852,149	November 24, 2015	Kimberly Chong
	14/857,555	April 12, 2016	Kimberly Chong
	14/857,555	November 6, 2015	Kimberly Chong
	14/857,561	April 18, 2016	Kimberly Chong
	14/857,561	March 15, 2016	Kimberly Chong
	14/857,561	February 17, 2016	Kimberly Chong
	14/857,561	January 8, 2016	Kimberly Chong
	14/857,561	October 23, 2015	Kimberly Chong
	14/858,250	November 6, 2015	Kimberly Chong
	12/605,276	June 18, 2014	J. McDonald
	12/605,276	October 18, 2013	J. McDonald
	12/605,276	December 23, 2011	J. McDonald
	12/605,276	August 24, 2011	J. McDonald
	12/605,276	February 11, 2011	J. McDonald
	13/829,545	June 6, 2014	J. McDonald
	13/830,253	June 11, 2014	J. McDonald
	13/830,253	November 26, 2013	J. McDonald
	14/523,610	May 11, 2016	J. McDonald
	14/852,257	October 27, 2015	J. McDonald
	14/852,257	October 6, 2015	J. McDonald
	14/852,264	April 21, 2016	J. McDonald
	14/852,264	October 21, 2015	J. McDonald
	14/857,569	May 6, 2016	J. McDonald
	14/857,569	November 19, 2015	J. McDonald
	14/857,590	May 16, 2016	J. McDonald
	14/857,590	November 19, 2015	J. McDonald
	14/858,416	May 4, 2016	J. McDonald
	14/858,416	October 27, 2015	J. McDonald
	14/214,567	July 7, 2016	E. Poliakova-Georgan
	14/214,567	December 3, 2015	E. Poliakova-Georgan
	14/214,567	June 24, 2015	E. Poliakova-Georgan
	14/213,607	September 15, 2015	D.H. Shin

Application No.: 15/705,172 (Information Disclosure Statement)

Docket No.: AVN-008CN41

	14/213,607	April 1, 2015	D.H. Shin
	14/213,607	September 18, 2014	D.H. Shin
	14/214,480	August 2, 2016	D.H. Shin
	14/214,480	October 19, 2015	D.H. Shin
	14/214,480	April 17, 2015	D.H. Shin
	14/214,480	September 19, 2014	D.H. Shin
	14/942,629	August 16, 2016	D.H. Shin
	13/509,331	September 16, 2013	T.A. Vivlemore
	13/509,331	January 28, 2013	T.A. Vivlemore
	14/108,137	April 29, 2015	T.A. Vivlemore
	14/108,137	October 9, 2015	T.A. Vivlemore
	14/108,137	October 3, 2014	T.A. Vivlemore
	14/944,886	April 27, 2017	T.A. Vivlemore
	14/944,886	September 30, 2016	T.A. Vivlemore
	14/213,641	August 1, 2016	D.H. Shin
	14/213,641	October 16, 2015	D.H. Shin
	14/213,641	March 31, 2015	D.H. Shin
	14/213,641	September 18, 2014	D.H. Shin
	14/213,629	May 23, 2016	E. Poliakova-Georgan
	14/213,629	August 21, 2015	E. Poliakova-Georgan
	14/213,629	December 29, 2014	E. Poliakova-Georgan
	14/743,856	August 1, 2016	A. Hudson Bowman
	14/776,533	February 28, 2017	D. Shin
	14/776,533	August 3, 2016	D. Shin
	15/274,719	December 16, 2016	K. Chong
	15/274,772	December 30, 2016	K. Chong
	15/274,772	September 18, 2017	K. Chong

The Examiner is requested to review the file histories of these applications, including cited references, Office Actions, Responses, etc., and is asked to contact Applicant's Attorney if the Examiner would like the Applicant to supply copies of any or all of the information included in any of these applications. For any of these applications, if Applicant's Attorney is not contacted by the Examiner with such a request, then it will be concluded that the Examiner has reviewed or will review the file content of these applications.

Applicant respectfully requests that the Examiner initial the blank columns next to the cited Applications and Office Actions, to indicate that the information has been considered by the Examiner. Alternatively, Applicant requests that the Examiner insert the phrase, "All references

Application No.: 15/705,172 (Information Disclosure Statement)

Docket No.: AVN-008CN41

considered except where lined through," on each page of the Information Disclosure Statement, along with the Examiner's initials.

The filing of this Information Disclosure Statement is not to be interpreted as a representation that the cited documents are material, that an exhaustive search has been conducted, or that no other relevant information exists. Nor shall the citation of any documents herein be construed *per se* as a representation that such document is prior art. Moreover, Applicant understands the Examiner will make an independent evaluation of the cited documents.

This Information Disclosure Statement is filed within three months of the U.S. filing date (37 C.F.R. § 1.97(b)(1)). Applicant believes no fee is due with this statement.

Dated: September 22, 2017

Respectfully submitted,

Electronic signature: /Amy E. Mandragouras, Esq./
Amy E. Mandragouras, Esq.
Registration No.: 36,207
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(617) 217-4626
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Attorney/Agent For Applicant

/KIMBERLY CHONG/ (10/01/2017)
10/01/2017

Doc code: IDS

36913

PTO/SB/08a (03-15)

Doc description: Information Disclosure Statement (IDS) Filed

Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	15705172
	Filing Date	2017-09-14
	First Named Inventor	Stephen Donald WILTON
	Art Unit	1674
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AVN-008CN41

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Application Number	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

1	University of Western Australia v. Academisch Ziekenhuis Leiden, Miscellaneous Order under 37 CFR 41.104(a), 4 pages, Patent Interference Nos. 106,007 and 106,008, dated December 15, 2014
2	University of Western Australia v. Academisch Ziekenhuis Leiden, Order - Authorizing Motions, Patent Interference No. 106,007, 3 pages, dated September 26, 2014 (Doc 20)
3	University of Western Australia v. Academisch Ziekenhuis Leiden, Order - Authorizing Motions, Patent Interference No. 106,007, 6 pages, dated September 23, 2014 (Doc 19)
4	University of Western Australia v. Academisch Ziekenhuis Leiden, Order - Authorizing Motions, Patent Interference No. 106,008, 6 pages, dated September 23, 2014 (Doc 18)
5	University of Western Australia v. Academisch Ziekenhuis Leiden, Order - Miscellaneous, 2 pages, Patent Interference Nos. 106,007, 106,008, 106,013, dated November 14, 2014
6	University of Western Australia v. Academisch Ziekenhuis Leiden, Order to Show Cause- 37 CFR§ 41.104(a), filed in Patent Interference No. 106,013, June 22, 2015, pages 1-3 (Doc 193).
7	University of Western Australia v. Academisch Ziekenhuis Leiden, Redecoration, Patent Interference No. 106,008, 2 pages, dated September 23, 2014 (Doc 19)
8	University of Western Australia v. Academisch Ziekenhuis Leiden, Second Declaration of Matthew J. A. Wood, M.D., D. PHIL., Patent Interference Nos. 106,007 and 106,008, 78 pages, dated February 17, 2015 (Exhibit Number 2116 filed in interferences 106,007 and 106,008, on February 17, 2015.
9	University of Western Australia v. Academisch Ziekenhuis Leiden, Statement Concerning Initial Settlement Discussions, 3 pages, Patent Interference No. 106,013, (Doc 136), dated December 30, 2014.
10	University of Western Australia v. Academisch Ziekenhuis Leiden, Statement Concerning Settlement Discussions, 3 pages, Patent Interference No. 106,007, (Doc 242), dated December 30, 2014.
11	University of Western Australia v. Academisch Ziekenhuis Leiden, Statement Concerning Settlement Discussions, 3 pages, Patent Interference No. 106,008, (Doc 246), dated December 30, 2014.

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

12	University of Western Australia v. Academisch Ziekenhuis Leiden, Statement Concerning Subsequent Settlement Discussions, filed in Patent Interference No. 106,013, August 24, 2015, pages 1-3 (Doc 195).
13	University of Western Australia v. Academisch Ziekenhuis Leiden, University of Western Australia Response to Order to Show Cause, filed in Patent Interference No. 106,013, July 20, 2015, pages 1-28 (Doc 194).
14	University of Western Australia v. Academisch Ziekenhuis Leiden, University of Western Australia Exhibit List as of April 10, 2015, filed in Patent Interference No. 106,007, April 10, 2015, pages 1-10 (Doc 456).
15	University of Western Australia v. Academisch Ziekenhuis Leiden, University of Western Australia Exhibit List as of April 10, 2015, filed in Patent Interference No. 106,008, April 10, 2015, pages 1-10 (Doc 464).
16	University of Western Australia v. Academisch Ziekenhuis Leiden, University of Western Australia Exhibit List as of April 3, 2015, filed in Interference 106007, April 3, 2015, pages 1-10 (Doc 431).
17	University of Western Australia v. Academisch Ziekenhuis Leiden, University of Western Australia Exhibit List as of April 3, 2015, filed in Interference 106008, April 3, 2015, pages 1-10 (Doc 439).
18	University of Western Australia v. Academisch Ziekenhuis Leiden, University of Western Australia Exhibit List as of April 3, 2015, filed in Interference 106013, April 3, 2015, pages 1-10 (Doc 153).
19	University of Western Australia v. Academisch Ziekenhuis Leiden, University of Western Australia Exhibit List As of October 29, 2015, filed in Patent Interference No. 106,013, October 29, 2015, pages 1-10 (Doc 199).
20	University of Western Australia v. Academisch Ziekenhuis Leiden, University of Western Australia Miscellaneous Motion 4 (to exclude evidence), filed in Patent Interference No. 106,007, April 10, 2015, pages 1-21 (Doc 455).
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22	University of Western Australia v. Academisch Ziekenhuis Leiden, University of Western Australia Opposition 1 (Regarding Patentability Under 35 U.S.C. § 102/103), 38 pages, Patent Interference No. 106,007, (Doc 393), dated February 17, 2015

Application Number # 36916	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

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26	University of Western Australia v. Academisch Ziekenhuis Leiden, University of Western Australia Opposition 3 (Regarding Patentability Under 35 U.S.C. § 101), 22 pages, Patent Interference No. 106,007, (Doc 395), dated February 17, 2015
27	University of Western Australia v. Academisch Ziekenhuis Leiden, University of Western Australia Opposition 3 (Regarding Patentability Under 35 U.S.C. § 101), 22 pages, Patent Interference No. 106,008, (Doc 404), dated February 17, 2015
28	University of Western Australia v. Academisch Ziekenhuis Leiden, University of Western Australia Opposition 4 (To deny entry of AZL's Proposed New Claims 104 and 105), 36 pages, Patent Interference No. 106,007, (Doc 397), dated February 17, 2015
29	University of Western Australia v. Academisch Ziekenhuis Leiden, University of Western Australia Opposition 4 (To deny entry of AZL's Proposed New Claims 30 and 31), 36 pages, Patent Interference No. 106,008, (Doc 405), dated February 17, 2015
30	University of Western Australia v. Academisch Ziekenhuis Leiden, University of Western Australia Reply 1 (to AZL Opposition 1), filed April 3, 2015 in Interference 106007, pages 1-28 (Doc 428).
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32	University of Western Australia v. Academisch Ziekenhuis Leiden, University of Western Australia Reply 1 (to Maintain the Interference) filed April 3, 2015 in Interference 106013, pages 1-17 (Doc 152).
33	University of Western Australia v. Academisch Ziekenhuis Leiden, University of Western Australia Reply 2 (to AZL Opposition 2) filed April 3, 2015 in Interference 106007, pages 1-22 (Doc 429)

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
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Application Number # 36917	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

34	University of Western Australia v. Academisch Ziekenhuis Leiden, University of Western Australia Reply 2 (to AZL Opposition 2) filed April 3, 2015 in Interference 106008, pages 1-22 (Doc 437).
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36	University of Western Australia v. Academisch Ziekenhuis Leiden, University of Western Australia Reply 3 (to Institute an Interference) filed April 3, 2015 in Interference 106007, pages 1-17 (Doc 430).
37	University of Western Australia v. Academisch Ziekenhuis Leiden, University of Western Australia Reply 4 (To Exclude Evidence), filed in Patent Interference No. 106,007, May 12, 2015, pages 1-13 (Doc 467).
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39	University of Western Australia v. Academisch Ziekenhuis Leiden, University of Western Australia Request for Oral Argument, filed in Patent Interference No. 106,007, April 10, 2015, pages 1-4 (Doc 457).
40	University of Western Australia v. Academisch Ziekenhuis Leiden, University of Western Australia Request for Oral Argument, filed in Patent Interference No. 106,008, April 10, 2015, pages 1-4 (Doc 465).
41	University of Western Australia v. Academisch Ziekenhuis Leiden, University of Western Australia Request for Oral Argument, filed in Patent Interference No. 106,013, April 10, 2015, pages 1-3 (Doc 190).
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**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number # 36918	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

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STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number # 36919	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Amy E. Mandragouras, Esq./	Date (YYYY-MM-DD)	2017-09-22
Name/Print	Amy E. Mandragouras, Esq.	Registration Number	36,207

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	Filing Date	2017-09-14
	First Named Inventor	Stephen Donald WILTON
	Art Unit	1674
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AVN-008CN41

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	1	2000-325085	JP	A	2000-11-28	MATSUO MASAFUMI, ET AL.		
	2	2002-010790	JP	A	2002-01-15	Matsuo Masafumi		×
	3	2002-325582	JP	A	2002-11-12	MATSUO, MASAFUMI, ET AL.		□

Application Number
30922

15705172

Filing Date

2017-09-14

First Named Inventor

Stephen Donald WILTON

Art Unit

1674

Examiner Name

Not Yet Assigned

Attorney Docket Number

AVN-008CN41

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

4	2002-340857	JP	A	2002-11-27	Matsushita Electric Ind Co Ltd	<input checked="" type="checkbox"/>
5	2002-529499	JP	A	2002-09-10	Eli Lilly and Company	<input checked="" type="checkbox"/>
6	2004-509622	JP	A	2004-04-02	Academisch Ziekenhuis Leiden	<input checked="" type="checkbox"/>
7	2010-268815	JP	A	2010-12-02	MATSUO MASAFUMI	<input type="checkbox"/>
8	2011-101655	JP	A	2011-05-26	Academisch Ziekenhuis Leiden	<input checked="" type="checkbox"/>
9	2011-200235	JP	A	2011-10-13	Academisch Ziekenhuis Leiden	<input checked="" type="checkbox"/>
10	2014-054250	JP	A	2014-03-27	Nippon Shinyaku Co Ltd,	<input checked="" type="checkbox"/>
11	2014-111638	JP	A	2014-06-19	Academisch, Ziekenhuis Leiden et al.	<input checked="" type="checkbox"/>
12	2014-138589	JP	A	2014-07-31	Academisch, Ziekenhuis Leiden	<input checked="" type="checkbox"/>
13	4777777	JP	B2	2011-09-21	Kobe University	<input checked="" type="checkbox"/>
14	4846965	JP	B2	2011-12-28	ACADEMISCH ZIEKENHUIS LEIDEN	<input type="checkbox"/>

Application Number
30923

15705172

Filing Date

2017-09-14

First Named Inventor

Stephen Donald WILTON

Art Unit

1674

Examiner Name

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Attorney Docket Number

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STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

15	5138722	JP	B2	2013-02-06	Matsuo Masafumi,	<input checked="" type="checkbox"/>
16	5378423	JP	B2	2013-12-25	ACADEMISCH ZIEKENHUIS LEIDEN	<input type="checkbox"/>
17	00/15780	WO	A1	2000-03-23	University College London	<input type="checkbox"/>
18	00/44897	WO	A1	2000-08-03	AVI Biopharma, Inc.	<input type="checkbox"/>
19	00/78341	WO	A1	2000-12-28	Murdoch Childrens Research Institute	<input type="checkbox"/>
20	01/49775	WO	A2	2001-07-12	AVI Biopharma, Inc.	<input type="checkbox"/>
21	01/72765	WO	A1	2001-10-04	ISIS Pharmaceuticals, Inc.	<input type="checkbox"/>
22	01/83503	WO	A2	2001-11-08	Hybridon, Inc	<input type="checkbox"/>
23	01/83740	WO	A2	2001-11-08	AVI Biopharma, Inc.	<input type="checkbox"/>
24	02/018656	WO	A2	2002-03-07	AVI Biopharma, Inc.	<input type="checkbox"/>
25	02/24906	WO	A1	2002-03-28	Academisch Ziekenhuis Leiden	<input type="checkbox"/>

Application Number # 30924		15705172
Filing Date		2017-09-14
First Named Inventor	Stephen Donald WILTON	
Art Unit	1674	
Examiner Name	Not Yet Assigned	
Attorney Docket Number	AVN-008CN41	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

26	02/29406	WO	A1	2002-04-11	Murto, James		<input type="checkbox"/>
27	03/053341	WO	A2	2003-07-03	Isis Pharmaceuticals, Inc.		<input type="checkbox"/>
28	04/048570	WO	A1	2004-06-10	Kobe University		<input checked="" type="checkbox"/>
29	04/083432	WO	A1	2004-09-30	Academisch Ziekenhuis Leiden		<input type="checkbox"/>
30	04/083446	WO	A2	2004-09-30	Academisch Ziekenhuis Leiden		<input type="checkbox"/>
31	2005/115479	WO	A2	2005-12-08	Avi Biopharma, Inc		<input type="checkbox"/>
32	2006/000057	WO	A1	2006-01-05	University of Western Australia		<input type="checkbox"/>
33	2006/021724	WO	A2	2006-03-02	Genethon et al.		<input checked="" type="checkbox"/>
34	2006/112705	WO	A2	2006-10-26	Academisch Ziekenhuis Leiden		<input type="checkbox"/>
35	2007/058894	WO	A2	2007-05-24	The University of North Carolina at Chapel Hill et		<input type="checkbox"/>
36	2007/133812	WO	A2	2007-11-22	Philadelphia Health & Education Corporation, D/B/A		<input type="checkbox"/>

Application Number
30925

15705172

Filing Date

2017-09-14

First Named Inventor

Stephen Donald WILTON

Art Unit

1674

Examiner Name

Not Yet Assigned

Attorney Docket Number

AVN-008CN41

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

37	2007/135105	WO	A1	2007-11-29	Academisch Ziekenhuis Leiden	<input type="checkbox"/>
38	2008/036127	WO	A2	2008-03-27	Avi Biopharma, Inc.	<input type="checkbox"/>
39	2009/054725	WO	A2	2009-04-30	Academisch Ziekenhuis Leiden et al.	<input type="checkbox"/>
40	2009/101399	WO	A1	2009-08-20	Isis Innovation Limited	<input type="checkbox"/>
41	2009/139630	WO	A2	2009-11-19	Prosensa Technologies B.V. et al.	<input type="checkbox"/>
42	2010/048586	WO	A1	2010-04-29	AVI Biopharma, Inc.	<input type="checkbox"/>
43	2010/050801	WO	A1	2010-05-06	Prosensa Technologies B.V. et al.	<input type="checkbox"/>
44	2010/050802	WO	A2	2010-05-06	Academisch Ziekenhuis Leiden et al.	<input type="checkbox"/>
45	2010/115993	WO	A1	2010-10-14	Association Institut de Myologie et al.	<input type="checkbox"/>
46	2010/123369	WO	A1	2010-10-28	Prosensa Technologies B.V.	<input type="checkbox"/>
47	2010/136415	WO	A1	2010-12-02	Universita Degli Studi di Roma "La Sapienza"	<input type="checkbox"/>

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

48	2010/136417	WO	A1	2010-12-02	Universita Degli Studi di Roma "La Sapienza"	<input type="checkbox"/>
49	2010/150231	WO	A1	2010-12-29	Universita Degli Studi di Ferrara	<input type="checkbox"/>
50	2011/024077	WO	A2	2011-03-03	Inserm (Institut National de la Sante et de la Rec	<input type="checkbox"/>

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	1	AON PS1966 Mass Spectrometry Data, Pages 8, Exhibit Number 1154 filed in Interferences 106,007 and 106,008 on February 16, 2015.	
	2	AON PS1966 UPLC Data, Pages 2, Exhibit Number 1165 filed in Interferences 106,007 and 106,008 on February 16, 2015.	
	3	AON PS1967 Mass Spectrometry Data, Pages 7, Exhibit Number 1155 filed in Interferences 106,007 and 106,008 on February 16, 2015.	
	4	AON PS1967 UPLC Data, Pages 2, Exhibit Number 1166 filed in Interferences 106,007 and 106,008 on February 16, 2015.	
	5	AON PS229 (h53AON1) HPLC Chromatograph Pages 2, Exhibit Number 1140 filed in Interferences 106,007 and 106,008 on February 16, 2015.	
	6	AON PS229 (h53AON1) HPLC Method Report, Pages 3, Exhibit Number 1139 filed in Interferences 106,007 and 106,008 on February 16, 2015.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number # 36927	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

7	AON PS229 (h53AON1) Mass Spectrometry Data, Pages 3, Exhibit Number 1142 filed in Interferences 106,007 and 106,008 on February 16, 2015.
8	AON PS229 (h53AON1) Synthesis Laboratory Notebook Entry, Pages 1, Exhibit Number 1137 filed in Interferences 106,007 and 106,008 on February 16, 2015.
9	AON PS229L (h53AON229L) Certificate of Analysis, Pages 1, Exhibit Number 1129 filed in Interferences 106,007 and 106,008 on February 17, 2015.
10	AON PS43 (h51AON1) Certificate of Analysis, Pages 1, Exhibit Number 1134 filed in Interferences 106,007 and 106,008 on February 16, 2015.
11	AON PS43 (h51AON1) HPLC Chromatogram, Pages 1, Exhibit Number 1131 filed in Interferences 106,007 and 106,008 on February 17, 2015.
12	AON PS43 (h51AON1) HPLC Method Report, Pages 4, Exhibit Number 1130 filed in Interferences 106,007 and 106,008 on February 17, 2015.
13	AON PS43 (h51AON1) Mass Spectrometry Data, Pages 3, Exhibit Number 1135 filed in Interferences 106,007 and 106,008 on February 16, 2015.
14	AON PS43 (h51AON1) UPLC-UV Data, Pages 2, Exhibit Number 1136 filed in Interferences 106,007 and 106,008 on February 16, 2015.
15	AONs PS1958, PS1959, PS1960, PS1961, PS1962, PS1963, PS1964, PS1965, PS1966, and PS1967 HPLC Method Report, Pages 3, Exhibit Number 1143 filed in Interferences 106,007 and 106,008 on February 16, 2015.
16	Applicant-Initiated Interview Summary dated April 8, 2013 in U.S. Application Serial No. 13/094,548, (University of Western Australia Exhibit 2144, filed April 3, 2015 in Interferences 106007, 106008, and 106013, pages 1-11).
17	Arechavala-Gomez V, et al., "Immunohistological intensity measurements as a tool to assess sarcolemma-associated protein expression," Neuropathol Appl Neurobiol 2010;36: 265-74.

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number # 36928	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

18	ARECHAVALA-GOMEZA, V. et al., "Comparative Analysis of Antisense Oligonucleotide Sequences for Targeted Skipping of Exon 51 During Dystrophin Pre-mRNA Splicing in Human Muscle," Human Gene Therapy, Vol. 18:798-810 (2007)
19	ARORA, Vikram et al., "c-Myc Antisense Limits Rat Liver Regeneration and Indicates Role for c-Myc in Regulating Cytochrome P-450 3A Activity," The Journal of Pharmacology and Experimental Therapeutics, Vol. 292(3):921-928 (2000)
20	Asetek Danmark A/S v. CMI USA, Inc., 2014 WL 5990699, N.D. Cal. 2014, 8 pages, (Academisch Ziekenhuis Leiden Exhibit 1237, filed May 5, 2015 in Interference 106007 and 106008).
21	ASVADI, Parisa et al., "Expression and functional analysis of recombinant scFv and diabody fragments with specificity for human RhD," Journal of Molecular Recognition, Vol. 15:321-330 (2002)
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25	AZL's U.S. Patent Application No. 14/295,311 and claims, as-filed June 3, 2014 ("the '311 Application") (Exhibit Number 1077 filed in interferences 106008, 106007 on December 23, 2014)
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Application Number
36929

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2017-09-14

First Named Inventor

Stephen Donald WILTON

Art Unit

1674

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STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

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Stephen Donald WILTON

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(Not for submission under 37 CFR 1.99)

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43	Claim Chart 11/233,495, Pages 57, Exhibit Number 1216 filed in Interferences 106,007 and 106,008 on February 17, 2015.
44	Claim Chart 13/550,210, Pages 45, Exhibit Number 1217 filed in Interferences 106,007 and 106,008 on February 17, 2015.
45	Claim Chart, US 7,807,816, 14 pages (Exhibit Number 1063 filed in interferences 106008, 106007 on November 18, 2014)
46	Claim Chart, US 7,960,541, 17 pages (Exhibit Number 1064 filed in interferences 106008, 106007 on November 18, 2014)
47	Claim Chart, US 8,455,636, 32 pages (Exhibit Number 1062 filed in interferences 106008, 106007 on November 18, 2014)
48	Claim Comparison Chart - Claims 11 and 29 in 13/550,210, Pages 1, Exhibit Number 1226 filed in Interferences 106,007 and 106,008 on February 17, 2015.
49	Claim Comparison Chart 13/550,210 vs 11/233,495, Pages 12, Exhibit Number 1218 filed in Interferences 106,007 and 106,008 on February 17, 2015.
50	Claim Comparison Chart 13/550,210 vs 12/198,007, Pages 1, Exhibit Number 1219 filed in Interferences 106,007 and 106,008 on February 17, 2015.

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Application Number # 36931	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

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STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number # 36932	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

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The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Amy E. Mandragouras, Esq./	Date (YYYY-MM-DD)	2017-09-22
Name/Print	Amy E. Mandragouras, Esq.	Registration Number	36,207

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	15705172
	Filing Date	2017-09-14
	First Named Inventor	Stephen Donald WILTON
	Art Unit	1674
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AVN-008CN41

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Application Number	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

1	Transcript of 2nd Deposition of Erik J. Sontheimer, Ph.D., dated March 12, 2015, (Academisch Ziekenhuis Leiden Exhibit 1231, filed April 3, 2015 in Interference 106007 and 106008, pages 1-185).
2	Transcript of 2nd Deposition of Matthew J.A. Wood, M.D., D. Phil, dated March 5, 2015, (Academisch Ziekenhuis Leiden Exhibit 1230, filed April 3, 2015 in Interference 106007 and 106008, pages 1-117).
3	Transcript of December 12, 2014 Teleconference with Administrative Patent Judge Schafer (rough draft) (previously filed in Int. No. 106,008 as Ex. 2114), Pages 28 Exhibit Number 1001 filed in Interference 106,013 on February 17, 2015.
4	Transcript of the January 21, 2015 deposition of Erik Sontheimer, Ph.D., Patent Interference Nos. 106,007 and 106,008, 98 pages, dated January 21, 2015 (Exhibit Number 2122 filed in interferences 106,007 and 106,008 on February 17, 2015).
5	Transcript of the March 11, 2015 deposition of Judith van Deutekom, Ph.D., (University of Western Australia Exhibit 2141, filed April 3, 2015 in Interferences 106007, 106008, and 106013, pages 1-168).
6	Transcript of the March 12, 2015 deposition of Erik J. Sontheimer, Ph.D., (University of Western Australia Exhibit 2142, filed April 3, 2015 in Interferences 106007, 106008, and 106013, pages 1-183).
7	Transcript of the March 5, 2015 deposition of Matthew J. A. Wood, M.D., D. PHIL., (University of Western Australia Exhibit 2146, filed April 3, 2015 in Interferences 106007, 106008, and 106013, pages 1-115).
8	Transfection of AON, Pages 1, Exhibit Number 1170 filed in Interferences 106,007 and 106,008 on February 16, 2015.
9	U.S. Food and Drug Administration Presentation at Peripheral and Central Nervous System Drugs Advisory Committee, April 25, 2016, 178 pages.
10	U.S. Food and Drug Administration Statement, dated December 30, 2014 (2 pages), Exhibit Number 1204 filed in Interferences 106,007 and 106,008 on February 17, 2015.
11	U.S. Patent Application No. 12/198,007, as-filed August 25, 2008 ("the '007 Application") (Exhibit Number 1073 filed in Interferences 106008, 106007 on December 23, 2014)

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
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Application Number # 36936	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

12	U.S. Patent Application No. 12/976,381, as-filed December 22, 2010 ("the '381 Application") (Exhibit Number 1074 filed in interferences 106008, 106007 on December 23, 2014)
13	U.S. Patent Application Publication No. 2001/0056077 ("Matsuo") (Exhibit Number 1080 filed in interferences 106008, 106007 on December 23, 2014)
14	U.S. Patent Application Publication No. 2002/0049173 ("Bennett et al.") (Exhibit Number 1081 filed in interferences 106008, 106007 on December 23, 2014)
15	U.S. Patent No. 5,190,931 ("the '931 Patent") (Exhibit Number 1069 filed in interferences 106008, 106007 on December 23, 2014)
16	U.S. Patent No. 7,001,761 (the "Xiao" Patent) (Exhibit Number 1070 filed in interferences 106008, 106007 on December 23, 2014)
17	University of Western Australia Objections to Opposition Evidence, served on February 24, 2015 filed in Interference No. 106,007, Exhibit 2150, filed April 10, 2015 in Interference Nos. 106007 and 106008, pages 1-15.
18	University of Western Australia Objections to Opposition Evidence, served on February 24, 2015, filed in Interference No. 106,008, Exhibit 2151, filed April 10, 2015, in Interference Nos. 106007 and 106008, pages 1-15.
19	University of Western Australia v. Academisch Ziekenhuis Leiden, Decision - Motions - 37 C.F.R. § 41.125(a), filed in Patent Interference No. 106008, September 20, 2016, pages 1-20 (Doc 480)
20	University of Western Australia v. Academisch Ziekenhuis Leiden, Decision - Motions - 37 CFR § 41.125(a) (Substitute), filed in Patent Interference No. 106007, May 12, 2016, pages 1-53 (Doc 476)
21	University of Western Australia v. Academisch Ziekenhuis Leiden, Judgment - Motions - 37 C.F.R. § 41.127 filed in Patent Interference No. 106008, September 20, 2016, pages 1-3 (Doc 481)
22	University of Western Australia v. Academisch Ziekenhuis Leiden, Judgment - Motions - 37 CFR § 41.127, filed in Patent Interference No. 106007, April 29, 2016, pages 1-3 (Doc 474)

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Application Number # 36937	15705172
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Art Unit	1674
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23	European Response, Application No. 13160338.3, 4 pages, dated June 26, 2014 (Exhibit Number 2085 filed in Interferences 106008, 106013, 106007 on November 18, 2014)
24	University of Western Australia v. Academisch Ziekenhuis Leiden, Redecaration - 37 CFR 41.203(c), filed in Patent Interference No. 106007, April 29, 2016, pages 1-2 (Doc 473)
25	University of Western Australia v. Academisch Ziekenhuis Leiden, Withdrawal and Reissue of Decision on Motions, filed in Patent Interference No. 106007, May 12, 2016, pages 1-2 (Doc 475)
26	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden List of Exhibits (as of Apr. 3, 2015), filed in Patent Interference No. 106,007, April 3, 2015, pages 1-18, (Doc 423).
27	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden List of Exhibits (as of Apr. 3, 2015), filed in Patent Interference No. 106,008, April 3, 2015, pages 1-18 (Doc 435).
28	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden List of Exhibits, 18 pages, Patent Interference No. 106,007, (Doc 391), dated February 17, 2015.
29	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden List of Exhibits, 18 pages, Patent Interference No. 106,008, (Doc 398), dated February 17, 2015.
30	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden List of Exhibits, 3 pages, Patent Interference No. 106,013, (Doc 147), dated February 17, 2015.
31	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden Notice of Service of Supplemental Evidence, 3 pages, Patent Interference No. 106,007 (Doc 414), dated March 9, 2015.
32	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden Notice of Service of Supplemental Evidence, 3 pages, Patent Interference No. 106,008 (Doc 422), dated March 9, 2015.
33	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden Opposition 1 (35 U.S.C. § 112(a)), 83 pages, Patent Interference No. 106,008, (Doc 400), dated February 17, 2015

**INFORMATION DISCLOSURE
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Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

34	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden Opposition 1 (35 U.S.C. § 112(a)), 93 pages, Patent Interference No. 106,007, (Doc 392), dated February 17, 2015
35	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden Opposition 1 (Standing Order ¶ 203.1 and 37 C.F.R. § 41.202(a) and (e)), 20 pages, Patent Interference No. 106,013, (Doc 148), dated February 17, 2015
36	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden Opposition 2 (Indefiniteness), 31 pages, Patent Interference No. 106,007, (Doc 396), dated February 17, 2015
37	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden Opposition 2 (Indefiniteness), 32 pages, Patent Interference No. 106,008, (Doc 401), dated February 17, 2015
38	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden Opposition 3 (35 U.S.C. § 135(b)), 44 pages, Patent Interference No. 106,008, (Doc 397), dated February 17, 2015
39	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden Opposition 3 (Standing Order § 203.1 and 37 C.F.R. § 41.202(a) and (e)), 20 pages, Patent Interference No. 106,007, (Doc 389), dated February 17, 2015.
40	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden Reply 1 (For Judgment that UWA's Claims are Unpatentable Under 35 U.S.C. §§ 102 and 103), dated April 3, 2015, filed in Patent Interference No. 106008, pages 1-17 (Doc 431).
41	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden Reply 1 (For Judgment that UWA's Claims are Unpatentable Under 35 U.S.C. §§ 102 and 103), dated April 3, 2015, filed in Patent Interference No. 106007, pages 1-17 (Doc 424).
42	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden Reply 2 (To Deny the Benefit of AU 2004903474), dated April 3, 2015, filed in Patent Interference No. 106007, pages 1-11(Doc 425).
43	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden Reply 2 (To Deny the Benefit of AU 2004903474), dated April 3, 2015, filed in Patent Interference No. 106008, pages 1-12 (Doc 432).
44	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden Reply 3 (For Judgment of Unpatentability based on Myriad) dated April 3, 2015, filed in Patent Interference No. 106007, pages 1-12 (Doc 426).

**INFORMATION DISCLOSURE
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Application Number # 36939	15705172
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First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

45	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden Reply 3 (For Judgment of Unpatentability based on Myriad) dated April 3, 2015, filed in Patent Interference No. 106008, pages 1-13 (Doc 433).
46	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden Reply 4 (In Support of Responsive Motion 4 to Add Two New Claims) dated April 3, 2015, filed in Patent Interference No. 106007, pages 1-17 (Doc 427).
47	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden Reply 4 (In Support of Responsive Motion 4 to Add Two New Claims) dated April 3, 2015, filed in Patent Interference No. 106008, pages 1-17 (Doc 434).
48	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden Request For Oral Argument, filed in Patent Interference No. 106,007, April 10, 2015, pages 1-3 (Doc 454).
49	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden Request For Oral Argument, filed in Patent Interference No. 106,008, April 10, 2015, pages 1-3 (Doc 462).
50	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden Responsive Motion 4 (To Add Two New Claims), 57 pages, Patent Interference No. 106,008, (Doc 245), dated December 23, 2014.

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That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Amy E. Mandragouras, Esq./	Date (YYYY-MM-DD)	2017-09-22
Name/Print	Amy E. Mandragouras, Esq.	Registration Number	36,207


This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

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The information provided by you in this form will be subject to the following routine uses:

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Search Notes 	Application/Control No. 15705172	Applicant(s)/Patent Under Reexamination WILTON ET AL.
	Examiner KIMBERLY CHONG	Art Unit 1674

CPC- SEARCHED		
Symbol	Date	Examiner
C07H 21/04	9/29/2017	KC

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

SEARCH NOTES		
Search Notes	Date	Examiner
SEQ ID No. 195	9/29/2017	KC
PALM inventor name search	9/29/2017	KC

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

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Doc code: IDS

#: 36943

PTO/SB/08a (03-15)

Doc description: Information Disclosure Statement (IDS) Filed

Approved for use through 07/31/2016. OMB 0651-0031

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	15705172
	Filing Date	2017-09-14
	First Named Inventor	Stephen Donald WILTON
	Art Unit	1674
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AVN-008CN41

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**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number # 36944	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

1	US Amendment After Non-Final Action for Application No. 11/233,495, 31 pages, dated June 24, 2010 (Exhibit Number 2073 filed in interferences 106008, 106013, 106007 on November 18, 2014)
2	US Amendment for Application No. 11/233,495, 15 pages, dated April 1, 2009 (Exhibit Number 2071 filed in interferences 106008, 106013, 106007 on November 18, 2014)
3	US Amendment for Application No. 11/233,495, 19 pages, dated October 31, 2007 (Exhibit Number 2070 filed in interferences 106008, 106013, 106007 on November 18, 2014)
4	US Amendment for Application No. 11/233,495, 19 pages, dated September 16, 2009 (Exhibit Number 2072 filed in interferences 106008, 106013, 106007 on November 18, 2014)
5	US Amendment for Application No. 11/233,495, 9 pages, dated October 31, 2007 (Exhibit Number 2070 filed in interferences 106008, 106013, 106007 on November 18, 2014)
6	US Amendment for Application No. 11/570,691, 9 pages, dated June 15, 2010 (Exhibit Number 1043 filed in interferences 106008, 106007 on November 18, 2014)
7	US Amendment for Application No. 13/271,080, 30 pages, dated January 30, 2013 (Exhibit Number 1049 filed in interferences 106008, 106007 on November 18, 2014)
8	US Amendment for Application No. 13/902,376, 36 pages, dated March 21, 2014 (Exhibit Number 1046 filed in interferences 106008, 106007 on November 18, 2014)
9	US Amendment in Response to Advisory Action for Application No. 11/233,495, 23 pages, dated March 14, 2011 (Exhibit Number 2074 filed in interferences 106008, 106013, 106007 on November 18, 2014)
10	US Amendments to the Claims for Application No. 11/233,495, 4 pages, dated May 8, 2014 (Exhibit Number 2077 filed in interferences 106008, 106013, 106007 on November 18, 2014)
11	US Amendments to the Claims for Application No. 14/198,992, 3 pages, dated July 16, 2014 (Exhibit Number 2079 filed in interferences 106008, 106013, 106007 on November 18, 2014)

Application Number # 36945	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

12	US Applicant-Initiated Interview Summary and Notice of Allowance for Application No. 13/550,210, 9 pages dated May 19, 2014 (Exhibit Number 2076 filed in interferences 106008, 106013, 106007 on November 18, 2014)
13	US application as-filed and Preliminary Amendment for Application No. 13/550,210, 59 pages dated July 16, 2012 (Exhibit Number 2087 filed in interferences 106008, 106013, 106007 on November 18, 2014)
14	US Application as-filed for application No. 14/198,992, 52 pages, dated March 6, 2014 (Exhibit Number 2086 filed in interferences 106008, 106013, 106007 on November 18, 2014)
15	US Application as-filed, Application Data Sheet, and Preliminary Amendment for Application No. 12/837,359, 101 pages, dated July 15, 2010 (Exhibit Number 2100 filed in interferences 106008, 106013, 106007 on November 18, 2014)
16	US Application for Letters Patent for Application No. 11/233,495 as-filed and preliminary amendment, 77 pages, dated September 21, 2005 (Exhibit Number 2095 filed in interferences 106008, 106013, 106007 on November 18, 2014)
17	US Application No. 11/233,495, 74 pages; excerpts of prosecution history for including: US Supplemental Amendment and Response dated May 8, 2014; Second Supplemental Response dated July 5, 2013; Supplemental Amendment dated June 26, 2013; Amendment after Non-final Action dated November 1, 2010; Amendment under 35 USC 1.114 dated September 16, 2009 (Exhibit Number 2054 filed in interferences 106008, 106013, 106007 on November 18, 2014)
18	US Application No. 14/198,992, 17 pages; excerpts of prosecution history including: Supplemental Amendment dated July 16, 2014; Response to Non-Final Office Action dated July 14, 2014 (Exhibit Number 2056 filed in interferences 106008, 106013, 106007 on November 18, 2014)
19	US Application No. 14/248,279, 29 pages; excerpts of prosecution history including: Amendment under 37 CFR 1.312 dated September 19, 2014; Amendment in Response to Final Office Action dated August 7, 2014; Declaration under 37 CFR 1.132 dated May 26, 2014; Declaration under 37 CFR 1.132 dated May 27, 2014; Response dated June 3, 2014 (Exhibit Number 2057 filed in interferences 106008, 106013, 106007 on November 18, 2014)
20	US Application No.13/550,210, 27 pages; excerpts of prosecution history including: Response and Amendment dated May 12, 2014; Response to Non-Final Office Action dated January 21, 2014; Second Preliminary Amendment dated January 3, 2013 (Exhibit Number 2055 filed in interferences 106008, 106013, 106007 on November 18, 2014)
21	US claim amendments for Application No. 13/550,210, 3 pages, dated May 12, 2014 (Exhibit Number 2078 filed in interferences 106008, 106013, 106007 on November 18, 2014)
22	US Claims for Application No. 12/976,381, 1 page, dated December 22, 2010 (Exhibit Number 2065 filed in interferences 106008, 106013, 106007 on November 18, 2014)

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number # 36946	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

23	US Declaration of Richard K. Bestwick, for Application No. 11/570,691, 5 pages, dated June 15, 2010 (Exhibit Number 1044 filed in interferences 106008, 106007 on November 18, 2014)
24	US E-mail from Patent Trial and Appeal Board to Danny Huntington, 2 pages, dated October 9, 2014 (Exhibit Number 2002 filed in interferences 106008 on October 17, 2014)
25	US Non-Final Office Action for Application No. 11/570,691, 16 pages, dated March 15, 2010 (Exhibit Number 1042 filed in interferences 106008, 106007 on November 18, 2014)
26	US Office Action for Application No. 13/271,080, 25 pages, dated July 30, 2012 (Exhibit Number 1048 filed in interferences 106008, 106007 on November 18, 2014)
27	US Office Action for Application No. 13/550,210, 12 pages, dated September 27, 2013 (Exhibit Number 2080 filed in interferences 106008, 106013, 106007 on November 18, 2014)
28	US Office Action for Application No. 13/902,376, 7 pages, dated January 7, 2014 (Exhibit Number 1045 filed in interferences 106008, 106007 on November 18, 2014)
29	US Patent Application No. 12/198,007 as-filed, 64 pages, dated August 25, 2008 (Exhibit Number 2092 filed in interferences 106008, 106013, and 106007 on November 18, 2014)
30	US Preliminary Amendment and application as-filed for Application No. 12/976,381, 64 pages, dated December 22, 2010 (Exhibit No. 2089 filed in Interferences 106007, 106008, and 106013 on November 18, 2014)
31	US Preliminary Amendment for Application No. 11/233,495, 10 pages, dated September 21, 2005 (Exhibit Number 2069 filed in interferences 106008, 106013, 106007 on November 18, 2014)
32	US Preliminary Remarks for Application No. 14/198,992, 1 page, dated March 6, 2014 (Exhibit Number 2097 filed in interferences 106008, 106013, 106007 on November 18, 2014)
33	US Proposed Terminal Disclaimer for Application No. 12/860,078, 2 pages, dated October 17, 2014 (Exhibit Number 2001 filed in interference 106008 on October 17, 2014)

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number # 36947	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

34	US Remarks for Application No. 14/248,279, 2 pages, dated August 27, 2014 (Exhibit Number 2110 filed in interferences 106008, 106013, 106007 on November 18, 2014)
35	US Response and amendments for Application No. 13/550,210, 12 pages, dated January 21, 2014 (Exhibit Number 2063 filed in interferences 106008, 106013, 106007 on November 18, 2014)
36	US Revised Figure 4H, US Application No. 13/271,080, 1 page (Exhibit Number 1050 filed in interferences 106008, 106007 on November 18, 2014)
37	US Terminal Disclaimer for Application No. 14/198,992, 1 page, dated July 15, 2014 (Exhibit Number 2096 filed in interferences 106008, 106013, 106007 on November 18, 2014)
38	US Terminal Disclaimer for Application No. 14/248,279, 1 page, dated August 7, 2014 (Exhibit Number 2109 filed in interferences 106008, 106013, 106007 on November 18, 2014)
39	US Track One Request, Application as-filed, and Application Data Sheet for Application No. 14/248,279, 68 pages, dated April 8, 2014 (Exhibit Number 2108 filed in interferences 106008, 106013, 106007 on November 18, 2014)
40	US Transmittal, application as-filed, and Preliminary Amendment for Application No. 11/570,691, 102 pages, dated December 15, 2006 (Exhibit Number 2103 filed in interferences 106008, 106013, 106007 on November 18, 2014)
41	US Transmittal, application as-filed, and Preliminary Amendment for Application No. 13/270,992, 101 pages, dated October 11, 2011 (Exhibit Number 2098 filed in interferences 106008, 106013, 106007 on November 18, 2014)
42	US Transmittal, application as-filed, and Preliminary Amendment for Application No. 13/271,080, 115 pages, dated October 11, 2011 (Exhibit Number 2111 filed in interferences 106008, 106013, 106007 on November 18, 2014)
43	US Updated Filing Receipt for Application No. 13/550,210, 3 pages, dated December 11, 2012 (Exhibit Number 2044 filed in interferences 106008, 106013, 106007 on November 18, 2014)
44	USPTO "2014 Procedure for Subject Matter Eligibility Analysis of Claims Reciting or Involving...Natural Products" ("the March Guidance"), 19 pages, (Exhibit Number 2118 filed in interferences 106,007 and 106,008 on February 17, 2015)

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number # 30948	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

45	USPTO Written Description Training Materials, Revised March 25, 2008, Example 12 (Exhibit Number 1068 filed in Interferences 106008, 106007 on December 23, 2014)
46	JWA Clean Copy of Claims and Sequence, as filed in Interference No. 106,007 on August 1, 2014 (Paper 12), 8 pages, (Exhibit Number 2126 filed in Interferences 106,007 and 106,008 on February 17, 2015).
47	JWA Clean Copy of Claims and Sequence, as filed in Interference No. 106,007 on August 7, 2014 (Paper 12), 8 pages, (Exhibit Number 2127 filed in Interferences 106,007 and 106,008 on February 17, 2015).
48	JWA Motion 1 (For Judgment Under 35 § 112(a)) from Int. No. 106,007 (PN 210), Pages 40, Exhibit Number 1005 filed in Interference 106,013 on February 17, 2015.
49	JWA Motion 1 (For Judgment Under 35 § 112(a)) from Int. No. 106,008 (Doc 213), Pages 38, Exhibit Number 1004 filed in Interference 106,013 on February 17, 2015.
50	JWA submission of teleconference transcript, 28 pages, dated December 12, 2014 (Exhibit Number 2114 filed in Interferences 106008 and 106007 on December 12, 2014)

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Examiner Signature	/KIMBERLY CHONG/ (10/01/2017)	Date Considered	10/01/2017
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Application Number
36949

15705172

**INFORMATION DISCLOSURE
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(Not for submission under 37 CFR 1.99)

Filing Date

2017-09-14

First Named Inventor

Stephen Donald WILTON

Art Unit

1674

Examiner Name

Not Yet Assigned

Attorney Docket Number

AVN-008CN41

CERTIFICATION STATEMENT

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Signature	/Amy E. Mandragouras, Esq./	Date (YYYY-MM-DD)	2017-09-22
Name/Print	Amy E. Mandragouras, Esq.	Registration Number	36,207

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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Doc code: IDS

36951

PTO/SB/08a (03-15)

Doc description: Information Disclosure Statement (IDS) Filed

Approved for use through 07/31/2016. OMB 0651-0031
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	15705172
	Filing Date	2017-09-14
	First Named Inventor	Stephen Donald WILTON
	Art Unit	1674
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AVN-008CN41

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Application Number # 36952	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

1	Valorization Memorandum published by the Dutch Federation of University Medical Centers in March 2009, (University of Western Australia Exhibit 2140, filed April 3, 2015 in Interferences 106007, 106008, and 106013, pages 1-33).
2	VAN DEUTEKOM et al., "Antisense-induced exon skipping restores dystrophin expression in DMD patient derived muscle cells," HUMAN MOLECULAR GENETICS Vol. 10, No. 15: 1547-1554 (2001) (Exhibit Number 1084 filed in Interferences 106008, 106007 on December 23, 2014)
3	van Deutekom et al., "Local Dystrophin Restoration with Antisense Oligonucleotide PRO051," N. Engl. J. Med., Vol. 357, No. 26, pp. 2677-2686 (December, 2007), Exhibit Number 1213 filed in Interferences 106,007 and 106,008 on February 17, 2015.
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Application Number # 36953	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

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(Not for submission under 37 CFR 1.99)

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Application Number # 36954	15705172
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First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

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STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

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First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

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(Not for submission under 37 CFR 1.99)

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**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
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Application Number # 36956	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

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Examiner Signature	/KIMBERLY CHONG/ (10/01/2017)	Date Considered	10/01/2017
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STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number # 36957	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Amy E. Mandragouras, Esq./	Date (YYYY-MM-DD)	2017-09-22
Name/Print	Amy E. Mandragouras, Esq.	Registration Number	36,207

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	15705172
	Filing Date	2017-09-14
	First Named Inventor	Stephen Donald WILTON
	Art Unit	1674
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AVN-008CN41

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Application Number # 36980	15705172
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First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

1	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden Responsive Motion 4 (To Add Two New Claims), 65 pages, Patent Interference No. 106,007, (Doc 241), dated December 23, 2014.
2	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden Statement Regarding Oral Argument, filed in Patent Interference No. 106,013, April 10, 2015, pages 1-3 (Doc 189).
3	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden's Opposition 4 (To Not Exclude Evidence), filed in Patent Interference No. 106,007, May 5, 2015, pages 1-22 (Doc 465).
4	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden's Opposition 4 (To Not Exclude Evidence), filed in Patent Interference No. 106,008, May 5, 2015, pages 1-21 (Doc 473).
5	University of Western Australia v. Academisch Ziekenhuis Leiden, Academisch Ziekenhuis Leiden's Second Supplemental Notice of Real Party in Interest, filed in Patent Interference No. 106,007, May 28, 2015, pages 1-3, (Doc 468)
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Application Number # 36961	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

12	University of Western Australia v. Academisch Ziekenhuis Leiden, AZL Annotated Copy of Claims, Patent Interference No. 106,007, 15 pages, dated August 15, 2014 (Doc 15)
13	University of Western Australia v. Academisch Ziekenhuis Leiden, AZL Annotated Copy of Claims, Patent Interference No. 106,008, 14 pages, dated August 21, 2014 (Doc 14)
14	University of Western Australia v. Academisch Ziekenhuis Leiden, AZL Annotated Copy of Claims, Patent Interference No. 106,013, 14 pages, dated October 27, 2014 (Doc 16)
15	University of Western Australia v. Academisch Ziekenhuis Leiden, AZL Clean Copy of Claims and Sequence, filed in Patent Interference No. 106,013, 5 pages, dated October 15, 2014 (Doc 12)
16	University of Western Australia v. Academisch Ziekenhuis Leiden, AZL Corrected Notice of Related Proceedings, Patent Interference No. 106,007, 3 pages, dated August 1, 2014 (Doc 13)
17	University of Western Australia v. Academisch Ziekenhuis Leiden, AZL Exhibit List, 10 pages, Patent Interference No. 106,007 dated December 23, 2014 (Doc 240)
18	University of Western Australia v. Academisch Ziekenhuis Leiden, AZL List of Exhibits, 9 pages, Patent Interference No. 106,007, dated November 18, 2014 (Doc 209)
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20	University of Western Australia v. Academisch Ziekenhuis Leiden, AZL List of Proposed Motions, Patent Interference No. 106,007, 6 pages, dated September 10, 2014 (Doc 16)
21	University of Western Australia v. Academisch Ziekenhuis Leiden, AZL List of Proposed Motions, Patent Interference No. 106,008, 8 pages, dated September 10, 2014 (Doc 15)
22	University of Western Australia v. Academisch Ziekenhuis Leiden, AZL Motion 1 (For Judgment that UWA's Claims are Unpatentable Under 35 U.S.C. sections 102 and 103), 69 pages, Patent Interference No. 106,007, dated November 18, 2014 (Doc 181)

Application Number # 36962	15705172
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First Named Inventor	Stephen Donald WILTON
Art Unit	1674
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23	University of Western Australia v. Academisch Ziekenhuis Leiden, AZL Motion 1 (For Judgment that UWA's Claims are Unpatentable Under 35 U.S.C. sections 102 and 103), 69 pages, Patent Interference No. 106,008, dated November 18, 2014 (Doc 184)
24	University of Western Australia v. Academisch Ziekenhuis Leiden, AZL Motion 2 (To Deny UWA the Benefit of AU 2004903474), 23 pages, Patent Interference No. 106,007, dated November 18, 2014 (Doc 26)
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26	University of Western Australia v. Academisch Ziekenhuis Leiden, AZL Motion 3 (For Judgment of Unpatentability based on Myriad) 20 pages, Patent Interference No. 106,008, dated November 18, 2014 (Doc 30)
27	University of Western Australia v. Academisch Ziekenhuis Leiden, AZL Motion 3 (For Judgment of Unpatentability based on Myriad), 19 pages, Patent Interference No. 106,007, dated November 18, 2014 (Doc 27)
28	University of Western Australia v. Academisch Ziekenhuis Leiden, AZL Notice of Related Proceedings, Patent Interference No. 106,007, 3 pages, dated July 31, 2014 (Doc 6)
29	University of Western Australia v. Academisch Ziekenhuis Leiden, AZL Notice of Related Proceedings, Patent Interference No. 106,008, 3 pages, dated August 5, 2014 (Doc 7)
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31	University of Western Australia v. Academisch Ziekenhuis Leiden, Clean Copy of Claims and Sequences, 5 pages, dated August 5, 2014 (Exhibit Number 2047 filed in interferences 106008, 106013, 106007 on November 18, 2014)
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33	University of Western Australia v. Academisch Ziekenhuis Leiden, Clean Copy of Claims and Sequences, 5 pages, dated October 15, 2014 (Exhibit Number 2050 filed in interferences 106008, 106013, 106007 on November 18, 2014)

**INFORMATION DISCLOSURE
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First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

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36	University of Western Australia v. Academisch Ziekenhuis Leiden, Decision- Priority 37 CFR § 41.125 (a), 18 pages, Patent Interference No. 106,013, (Doc 196), dated September 29, 2015.
37	University of Western Australia v. Academisch Ziekenhuis Leiden, Decision-Rehearing -37 CFR § 41.125(c), filed in Patent Interference No. 106,013, December 29, 2015, pages 1-12 (Doc 202).
38	University of Western Australia v. Academisch Ziekenhuis Leiden, Declaration of Erik Sontheimer dated November 17, 2014, Exhibit 1012 filed in Patent Interference Nos. 106,007 and 106,008, 112 pages, filed November 18, 2014
39	University of Western Australia v. Academisch Ziekenhuis Leiden, Declaration of Interference, Patent Interference No. 106,007, 7 pages, dated July 18, 2014 (Doc 1)
40	University of Western Australia v. Academisch Ziekenhuis Leiden, Declaration of Interference, Patent Interference No. 106,008, 7 pages, dated July 24, 2014 (Doc 1)
41	University of Western Australia v. Academisch Ziekenhuis Leiden, Declaration of Interference, Patent Interference No. 106,013, 8 pages, dated September 29, 2014 (Doc 1)
42	University of Western Australia v. Academisch Ziekenhuis Leiden, Declaration of Matthew J.A. Wood, Patent Interference Nos. 106,007, 106,008 and 106,013, 184 pages, dated November 18, 2014 (Exhibit Number 2081 filed in Interferences 106008, 106013, 106007 on November 18, 2014)
43	University of Western Australia v. Academisch Ziekenhuis Leiden, Joint Stipulation regarding Time Periods 2, 3 and 4, 3 pages, Patent Interference No. 106,013, (Doc 135), dated January 25, 2015.
44	University of Western Australia v. Academisch Ziekenhuis Leiden, Joint Stipulation regarding Time Periods 3-4, 4 pages, Patent Interference No. 106,007, (Doc 243), dated January 29, 2015.

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number # 36964	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

45	University of Western Australia v. Academisch Ziekenhuis Leiden, Joint Stipulation regarding Time Periods 3-4, 4 pages, Patent Interference No. 106,008, (Doc 247), dated January 29, 2015.
46	University of Western Australia v. Academisch Ziekenhuis Leiden, Joint Stipulation regarding Time Periods 3-4, 4 pages, Patent Interference No. 106,013, (Doc 137), dated January 29, 2015.
47	University of Western Australia v. Academisch Ziekenhuis Leiden, Joint Stipulation Regarding Time Periods 4-6, 4 pages, Patent Interference No. 106,007, dated March 19, 2015 (Doc 416)
48	University of Western Australia v. Academisch Ziekenhuis Leiden, Joint Stipulation Regarding Time Periods 4-6, 4 pages, Patent Interference No. 106013, (Doc 151), dated March 19, 2015.
49	University of Western Australia v. Academisch Ziekenhuis Leiden, Joint Stipulation Regarding Time Periods 4-6, 4 pages, Patent Interference No. 106,008, (Doc 424), dated March 19, 2015.
50	University of Western Australia v. Academisch Ziekenhuis Leiden, Judgment-37 CFR § 41.127, 2 pages, Patent Interference No. 106,013, (Doc 197), dated September 29, 2015.

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature	/KIMBERLY CHONG/ (10/01/2017)	Date Considered	10/01/2017
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

Application Number # 36965	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	Not Yet Assigned
Attorney Docket Number	AVN-008CN41

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Amy E. Mandragouras, Esq./	Date (YYYY-MM-DD)	2017-09-22
Name/Print	Amy E. Mandragouras, Esq.	Registration Number	36,207

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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BIB DATA SHEET

CONFIRMATION NO. 2879

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.		
15/705,172	09/14/2017	514	1674	AVN-008CN41		
RULE						
APPLICANTS The University of Western Australia, Crawley, AUSTRALIA; INVENTORS Stephen Donald WILTON, Applecross, AUSTRALIA; Sue FLETCHER, Bayswater, AUSTRALIA; Graham MCCLOREY, Bayswater, AUSTRALIA; ** CONTINUING DATA ***** This application is a CON of 15/274,772 09/23/2016 which is a CON of 14/740,097 06/15/2015 PAT 9605262 which is a CON of 13/741,150 01/14/2013 ABN which is a CON of 13/168,857 06/24/2011 ABN which is a CON of 12/837,359 07/15/2010 PAT 8232384 which is a CON of 11/570,691 01/15/2008 PAT 7807816 which is a 371 of PCT/AU2005/000943 06/28/2005 ** FOREIGN APPLICATIONS ***** AUSTRALIA 2004903474 06/28/2004 ** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** ** SMALL ENTITY ** 09/25/2017						
Foreign Priority claimed <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No 35 USC 119(a-d) conditions met <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Verified and Acknowledged <u>/KIMBERLY CHONG/</u> Examiner's Signature		<input type="checkbox"/> Met after Allowance Initials	STATE OR COUNTRY AUSTRALIA	SHEETS DRAWINGS 22	TOTAL CLAIMS 2	INDEPENDENT CLAIMS 2
ADDRESS Nelson Mullins Riley & Scarborough LLP/Sarepta One Post Office Square Boston, MA 02109 UNITED STATES						
TITLE ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF						
FILING FEE RECEIVED 730	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:			<input type="checkbox"/> All Fees <input type="checkbox"/> 1.16 Fees (Filing) <input type="checkbox"/> 1.17 Fees (Processing Ext. of time) <input type="checkbox"/> 1.18 Fees (Issue) <input type="checkbox"/> Other _____ <input type="checkbox"/> Credit		

Office of Petitions: Routing Sheet



Application No. 15/705,172

This application is being forwarded to your office for further processing. A decision has been rendered on a petition filed in this application, as indicated below. For details of this decision, please see the document PET.OP.DEC filed on the same date as this document.

☒ **GRANTED**

☐ **DISMISSED**

☐ **DENIED**

Office of Petitions: Decision Count Sheet

Mailing Month

Application No.

15705172



For US serial numbers: enter number only, no slashes or commas. Ex: 10123456

For PCT: enter "51+single digit of year of filing+last 5 numbers", Ex. for PCT/US05/12345, enter 51512345

Deciding Official:

ELGART, VANITHA

Count (1) - Palm Credit

15/705,172

Decision: GRANT

FINANCE WORK NEEDED

☐ Select Check Box for YES

Decision Type: 643 - Track One request



Notes:

Count (2)

Decision: n/a

FINANCE WORK NEEDED

☐ Select Check Box for YES

Decision Type: NONE

Notes:

Count (3)

Decision: n/a

FINANCE WORK NEEDED

☐ Select Check Box for YES

Decision Type: NONE

Notes:

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/705,172	09/14/2017	Stephen Donald WILTON	AVN-008CN41	2879

123147 7590 10/06/2017
Nelson Mullins Riley & Scarborough LLP/Sarepta
One Post Office Square
Boston, MA 02109

EXAMINER

CHONG, KIMBERLY

ART UNIT	PAPER NUMBER
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1674

NOTIFICATION DATE	DELIVERY MODE
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10/06/2017

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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chris.schlauch@nelsonmullins.com
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Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.:15/705,172
<p>1. THE REQUEST FILED <u>September 14, 2017</u> IS GRANTED.</p> <p>The above-identified application has met the requirements for prioritized examination</p> <p>A. <input checked="" type="checkbox"/> for an original nonprovisional application (Track I).</p> <p>B. <input type="checkbox"/> for an application undergoing continued examination (RCE).</p> <p>2. The above-identified application will undergo prioritized examination. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:</p> <p>A. filing a <u>petition for extension of time</u> to extend the time period for filing a reply;</p> <p>B. filing an <u>amendment to amend the application to contain more than four independent claims, more than thirty total claims</u>, or a multiple dependent claim;</p> <p>C. filing a <u>request for continued examination</u>;</p> <p>D. filing a notice of appeal;</p> <p>E. filing a request for suspension of action;</p> <p>F. mailing of a notice of allowance;</p> <p>G. mailing of a final Office action;</p> <p>H. completion of examination as defined in 37 CFR 41.102; or</p> <p>I. abandonment of the application.</p> <p>Telephone inquiries with regard to this decision should be directed to Vanitha Elgart at 571-272-7395.</p> <p>/Vanitha Elgart/ Vanitha Elgart [Signature]</p> <p>Petitions Examiner, Office of Petitions (Title)</p>	

To: chris.schlauch@nelsonmullins.com,ipqualityassuranceboston@nelsonmullins.com,ipboston.docketing@nelsonmullins.com
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15705172	CTNF	10/05/2017	AVN-008CN41
	1449	10/05/2017	AVN-008CN41
	1449	10/05/2017	AVN-008CN41
	1449	10/05/2017	AVN-008CN41
	1449	10/05/2017	AVN-008CN41
	1449	10/05/2017	AVN-008CN41
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	1449	10/05/2017	AVN-008CN41
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	1449	10/05/2017	AVN-008CN41
	1449	10/05/2017	AVN-008CN41

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Application	Document	Mailroom Date	Attorney Docket No.
15705172	PET.OP.DEC	10/06/2017	AVN-008CN41

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/705,172	09/14/2017	Stephen Donald WILTON	AVN-008CN41

CONFIRMATION NO. 2879

123147

Nelson Mullins Riley & Scarborough LLP/Sarepta
One Post Office Square
Boston, MA 02109

PUBLICATION NOTICE



Title: ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

Publication No. US-2018-0002697-A1

Publication Date: 01/04/2018

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently <http://www.uspto.gov/patft/>.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently <https://portal.uspto.gov/pair/PublicPair>. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

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Dated: January 5, 2018
Electronic Signature for Amy E. Mandragouras, Esq.: /Amy E. Mandragouras, Esq./

Docket No.: AVN-008CN41
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Stephen Donald Wilton *et al.*

Application No.: 15/705,172

Confirmation No.: 2879

Filed: September 14, 2017

Art Unit: 1674

For: ANTISENSE OLIGONUCLEOTIDES FOR
INDUCING EXON SKIPPING AND
METHODS OF USE THEREOF

Examiner: K. Chong

MS Amendment
Commissioner for Patents
P.O. Box 1450
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AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION UNDER
37 C.F.R. § 1.111

Dear Sir:

In response to the Office Action dated October 5, 2017 (Paper No. 20171001), please amend the above-identified U.S. patent application as follows:

The **Listing of the Claims** begins on page 2 of this paper.

Remarks/Arguments begin on page 3 of this paper.

Application No.: 15/705,172

Docket No.: AVN-008CN41

LISTING OF THE CLAIMS

1. **(Canceled)**
2. **(Previously Presented)** An antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69), wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide induces exon 53 skipping; or a pharmaceutically acceptable salt thereof.
3. **(Previously Presented)** A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69), wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide induces exon 53 skipping, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

Application No.: 15/705,172

Docket No.: AVN-008CN41

REMARKS

Claims 2 and 3 are pending in the application. Applicants respectfully request reconsideration and withdrawal of the rejections as discussed below. Should the Examiner agree, she is urged to call the undersigned to address any outstanding double patenting rejections to expedite prosecution of this application.

Claim Rejections - 35 USC § 103

Claims 2 and 3 are rejected under 35 U.S.C. 103(a) as being obvious over van Ommen *et al.* (WO 2004/083432) and Koenig *et al.* (Nature 338, 509 - 511 06 April 1989). Applicants respectfully traverse this rejection based on the following remarks.

The Office failed to establish a prima facie case of obviousness

The Office bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. (MPEP §2142, 9th Ed.) “The Federal Circuit has stated that ‘rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.’” (*Id.* citing *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006); see also *KSR*, 550 U.S. at 418, 82 USPQ2d at 1396 (quoting Federal Circuit statement with approval).)

“Obviousness is a question of law with underlying factual findings, including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the pertinent art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence such as commercial success, long-felt need, and the failure of others.” (*KSR Int’l Co. V. Teleflex, Inc.*, 550 U.S. 398 (2007) citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).) With respect to the third inquiry, to establish a *prima facie* case of obviousness, the Office must identify both a reason why a person of ordinary skill in the art would have combined the prior art elements to arrive at the claimed subject matter, and a reason why one of ordinary skill in the art would have considered the outcome predictable. (*KSR Int’l Co. V. Teleflex, Inc.*, 550 U.S. 398 (2007).)

“In cases involving the patentability of a new chemical compound, *prima facie* obviousness under the third *Graham* factor generally turns on the structural similarities and differences between the claimed compound and the prior art compounds.” According to

Application No.: 15/705,172

Docket No.: AVN-008CN41

established Federal Circuit precedent, a two-part "lead compound" analysis must be satisfied to establish a *prima facie* case of obviousness. (*Otsuka Pharmaceutical Co. Ltd., v. Sandoz, Inc.*, 678 F.3d 1280 (2012).) To satisfy the lead compound analysis, the Office must establish: (1) that one of ordinary skill in the art would have selected the asserted prior art compound as a lead compound for further development, and (2) that the prior art would have motivated one of ordinary skill in the art to modify the lead compound to make the claimed compound with a reasonable expectation of success. (*Id.* at 1291-1292.)

For the reasons below, neither prong of the two part inquiry has been met in the present case. The first prong is not met because the Office failed to provide a reason why one of ordinary skill in the art would have selected SEQ ID NO: 29 ("h53AON1") of van Ommen et al. as a lead compound. The second prong is not met because, even assuming that one of skill in the art would have selected h53AON1 as a lead compound, the Office failed to provide a reason or motivation to specifically **lengthen** h53AON1 by **nine** additional bases of SEQ ID NO: 195 to arrive at the limitation of claim 1 that the base sequence comprises at least 12 consecutive bases of SEQ ID NO: 195.¹ Moreover, there was a significant level of unpredictability associated with selecting a specific antisense oligonucleotide to induce effective exon skipping of human dystrophin pre-mRNA at the time of the invention, and therefore no reasonable expectation of success.

Lead Compound Analysis

i. **The Office failed to provide a reason why a person of ordinary skill in the art would have selected h53AON1 as a lead compound**

A lead compound is "a compound in the prior art that would be most promising to modify in order to improve upon its...activity and obtain a compound with better activity." (*Otsuka Pharmaceutical Co. Ltd., v. Sandoz, Inc.*, at 1291 (citing *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007)).) "[A] reason to select a compound as a lead compound depends on **more than just structural similarity**..." *Bristol-Myers Squibb Co. v. Teva Pharmaceuticals USA, Inc.*, 923 F.Supp.2d 602 at 657 (2013) (citing *Matrix Labs.*, 619 F.3d at 1354; emphasis added). Notably, it has been held that "absent

¹ Applicants note and further explain below that, contrary to the position of the Office, the skilled artisan must lengthen h53AON1 by nine nucleotides, not two nucleotides, of SEQ ID NO: 195 to achieve the requirement of at least 12 bases of SEQ ID NO: 195 recited by the instant claims.

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a reason or motivation based on such prior art evidence, *mere structural similarity* between a prior art compound and the claimed compound *does not inform the lead compound selection.*" (*Otsuka Pharmaceutical Co. Ltd., v. Sandoz, Inc.*, at 1292 (citing *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010)); emphasis added.)

The Office has not provided any evidence or reasoning to support the conclusion that a person of ordinary skill in the art would have selected h53AON1 as the lead compound. Instead, the Office simply chooses it as its basis for the alleged obviousness of the claimed subject matter. Thus, its' selection by the Office in the absence of any supporting evidence or reasoning as a lead compound can only be through impermissible hindsight. Accordingly, the Office has not established that a person of ordinary skill in the art would select h53AON1 as the lead compound to modify to arrive at the claimed antisense oligonucleotides. For this reason alone, the claims are not *prima facie* obvious over the cited documents, and the Office should therefore withdraw the rejection.

ii. *The cited art does not motivate a person of ordinary skill in the art to modify h53AON1 to make the claimed antisense oligonucleotides with a reasonable expectation of success*

Even if the Office had established that a person of ordinary skill in the art would have selected h53AON1 as the lead compound, the second prong of the test also has not been met. The second prong of the lead compound analysis requires a determination of whether "the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound with a reasonable expectation of success." (*Otsuka Pharmaceutical Co. Ltd., v. Sandoz, Inc.*, 678 F.3d at 1292 (2012).)

The Office relies on van Ommen et al. as teaching a genus of oligonucleotides 16-50 bases in length that are complementary to, and cause skipping of, exon 53, and selects SEQ ID NO: 29 (h53AON1), which it contends is a 18-mer oligonucleotide having a sequence identical to three nucleotides of SEQ ID NO: 195. The Office contends, "[i]t would have been obvious for one of ordinary skill in the art to make an antisense oligonucleotide of 20-31 bases" using "the sequence of h53AON1 to arrive at an oligonucleotide of 20 nucleotides and having 12 nucleotides of SEQ ID No. 195. . ." by "preparing obvious variants of h53AON1 to try to optimize the activity of the oligonucleotide. . ." using "common and efficient strategies" such as

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synthesizing and testing “longer oligonucleotides containing within them” h53AON1. (See Office Action at pages 4-5 (emphasis added).)

Applicants submit that a person of ordinary skill in the art would not have been motivated to modify h53AON1 of van Ommen et al. to arrive at the claimed morpholino antisense oligonucleotides, and certainly not with a reasonable expectation of success. Notably, none of the cited documents would have motivated one of ordinary skill in the art to *increase the length* of the 18-mer h53AON1 to 27 bases 100% complementary to the exon 53 target region +23 to +69 and, let alone select at least 12 consecutive bases of SEQ ID NO: 195 and *thymine bases* in place of uracil bases, and select a *morpholino* chemistry backbone rather than a 2'-O-methyl phosphorothioate ("2'-O-Me-PS").²

Importantly, Applicants respectfully point out that the Office’s proposed strategy for modification of h53AON1 by lengthening it by only two bases would not result in an antisense oligonucleotide within the scope of the instant claims. To illustrate this point, Applicants provide the following alignment of h53AON1 (line 2) to SEQ ID NO: 195 (line 1).

1.	<u>CUGAAGGUGUUCUUGUACUUCAUCC</u>	SEQ ID NO: 195
2.	CUGUUGCCUCCGGUUC <u>UG</u>	h53AON1
3.	CUGUUGCCUCCGGUUC <u>UGAA</u>	h53AON1+2 bases = 20mer
4.	CUGUUGCCUCCGGUUC <u>CUGAAGGUGUUC</u>	h53AON1+9 bases = 27mer

As can be seen from above and acknowledged by the Office, h53AON1 comprises only three consecutive bases of SEQ ID NO: 195 indicated in the underlined portion of lines 1 and 2. Addition of two additional consecutive bases to h53AON1 as proposed by the Office results in a 20mer that is within the claimed length range, but such a 20mer would only comprise five consecutive bases of SEQ ID NO: 195 as illustrated in line 3 – not at least 12 consecutive bases of SEQ ID NO: 195 as required by the claims. Applicants note that to achieve an antisense oligonucleotide of the instant claims comprising, *inter alia*, at least 12 bases of SEQ ID NO: 195, the skilled artisan would need to, *inter alia*, lengthen h53AON1 by 9 bases as illustrated in the underlined portion of line 4 above. Meaning, simply lengthening h53AON1 by two bases as suggested by the Office would clearly not result in the claim requirement of at least 12 bases of

² Nor can it be found that the claimed invention would have been “obvious to try” as there are *not a “finite number of identified, predictable solutions”* such that one ordinarily skilled in the art could have pursued known potential solutions with a reasonable expectation of success. (*Examination Guidelines Update: Developments in the Obviousness Inquiry after KSR v. Teleflex*, issued by the United States Patent and Trademark Office (Federal Register, Vol. 75, No. 169: 53643, September 1, 2010); emphasis added.)

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SEQ ID NO: 195. Applicants base the remainder of the response based on modifying h53AON1 by, *inter alia*, adding 9 consecutive bases of SEQ ID NO: 195.

With regard to van Ommen et al., it cannot be said that there were a "finite number" of known, predictable solutions to the problem of designing a more efficient exon skipping antisense oligonucleotide with a reasonable expectation of success. In fact, van Ommen et al. suggest a wide variety of modifications to the antisense oligonucleotide structure with little specificity as to any individual oligonucleotide in the following:

[t]he complementary oligonucleotide generated through a method of the invention is preferably complementary to a consecutive part of between **16 and 50 nucleotides** of the exon RNA. **Different types of nucleic acid may be used** to generate the oligonucleotide. Preferably, the oligonucleotide comprises RNA, as RNA/RNA hybrids are very stable. Since one of the aims of the exon skipping technique is to direct splicing in subjects, it is preferred that the oligonucleotide RNA comprises a **modification providing the RNA with an additional property**, for instance, resistance to endonucleases and RNaseH, additional hybridization strength, increased stability (for instance, in a bodily fluid), increased or decreased flexibility, reduced toxicity, increased intracellular transport, and/or tissue-specificity, etc. Preferably, the modification comprises a 2'-O-methyl-phosphorothioate oligoribonucleotide modification.

With the advent of **nucleic acid-mimicking technology**, it has become possible to generate molecules that have a similar, preferably the same, hybridization characteristics, in kind, not necessarily in amount, as nucleic acid itself. Such equivalents are, of course, also part of the invention. **Examples of such mimics** equivalents are **peptide nucleic acid, locked nucleic acid and/or a morpholino phosphorodiamidate**. . . . **Hybrids between one or more of the equivalents among each other and/or together** with nucleic acid are, of course, also part of the invention. In a preferred embodiment, an equivalent comprises locked nucleic acid, as locked nucleic acid displays a higher target affinity and reduced toxicity and, therefore, shows a higher efficiency of exon skipping. (van Ommen et al. page 9, line 28 to page 11, line 2; emphasis added.)

van Ommen et al. also teach that "[i]t is thus not absolutely required that all the bases in the region of complementarity are capable of pairing with bases in the opposing strand... **[m]ismatches may to some extent be allowed**." (van Ommen et al. at page 3, ll. 3-8; emphasis added.) van Ommen et al. does not require that additional bases added to the antisense oligonucleotide be complementary to exon 53. *Id.*

Thus, there are a tremendous number of possible solutions to modify h53AON1 based on the length and position of "16-50 bases," mismatches, and many possible variations at any of three "substituents" (*i.e.*, nucleobase, ribose ring and phosphate linkage). Even if one focuses on

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the nucleobase sequence, assumes the chemical backbone and internucleotide linkages are unmodified, and limits the number of possible bases to those found in RNA, as shown in h53AON1, adding a single nucleobase to a 18-mer yields 8 possible sequence combinations (A, C, G, or U added before or after the 18-mer.)³ Adding two nucleobases yields 64 possible combinations. Adding three nucleobases yields 256 combinations. Adding 9 nucleobases to obtain a 27-mer yields 2,621,440 possible combinations. And, adding 32 nucleobases to obtain a 50-mer yields 608,742,554,432,415,200,000 possible combinations.

Of course, this significantly *underestimates* the number of possible nucleobase combinations because van Ommen et al. specify "different types of nucleic acid," and is not limited to the "natural" bases A, C, G, and U found in RNA, but includes other naturally-occurring and non-naturally occurring nucleobases such as inosine, hypoxanthine, xanthine, and many others. Different types of nucleic acid also include nucleotide analogs and chemical modifications to the backbone, as all of the working examples by van Ommen et al. use 2'-O-Me-PS oligoribonucleotide modifications. Different types of nucleic acid also include "mimetics" such as peptide nucleic acids, locked nucleic acid, and morpholino phosphorodiamidates. (van Ommen et al. at page 10, ll. 11-16.) Given the incredibly large number of modifications to h53AON1 that are taught by the cited documents the only way to start from h53AON1 and modify it to arrive at the claimed antisense oligonucleotide is by the application of hindsight.

There is also no reason or motivation to specifically *increase* the length of h53AON1 as there is no teaching in van Ommen et al. with respect to the effects on exon skipping of *lengthening* (or shortening) an antisense oligonucleotide. In fact, as shown in Table 2, all of the antisense oligonucleotides with exon skipping activity are **15-24 bases in length**, and all but 3 of those are between **17 and 20 bases**, almost two thirds are either **19 or 20 bases**, and **none are 25 bases in length**. (van Ommen et al. Table 2 at page 48.) As the vast majority of the antisense oligonucleotides tested by van Ommen et al. in Table 2 are **20 bases or less** (25/30), one of ordinary skill in the art would have no reason or motivation to lengthen h53AON1 at all. In fact, one skilled in the art would be equally motivated to shorten h53AON1, as almost two thirds of

³ Assuming only the four RNA nucleobases, the number of nucleobase combinations for a particular length AON can be calculated by this formula, where "n" equals the number of bases being added to the chain: $(4^n) \times (n+1)$. This is because each additional nucleotide can be added to either end of SEQ ID NO: 29.

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the antisense oligonucleotides are either 19 or 20 bases, and the shortest antisense oligonucleotide with activity in Table 2 is 15 bases (h46AON4b).

Moreover, the Office failed to provide a reason why the skilled artisan would lengthen h53AON1. Instead, the Office merely concludes the skilled artisan would “prepare obvious variants of h53AON1 to try to optimize the activity of the oligonucleotide” and that the skilled artisan would “try” to enhance activity by “a common and efficient strategy” of synthesizing and testing “longer oligonucleotides containing within them the sequence known to have the desired activity.” Office Action at pages 4-5. The Office overlooks the fact that in Table 2 the only other antisense oligonucleotide made and tested by van Ommen et al. is h53AON2, and this antisense oligonucleotide – like h53AON1 – is an 18mer. Applicants respectfully point out that “[a] particular parameter must first be *recognized* as a *result-effective variable*, i.e., a variable which achieves a *recognized* result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation.” M.P.E.P. 2144.05(II)(B) (emphasis added); see also *In re Antonie*, 559 F.2d 618, 195 U.S.P.Q. 6 (CCPA 1977).

In the present case, the Office failed to satisfy its burden of providing evidence that oligonucleotide length was recognized in the prior art as a result effective variable for exon 53 skipping and activity in treatment for DMD. See *id.* Absent such evidence of recognition as a “result-effective variable[,]” it is not, therefore, routine optimization “within the skill of the artisan” to vary the length of an oligonucleotide to optimize exon 53 skipping and activity in the treatment of DMD. See M.P.E.P. 2144.05(II)(B); *In re Antonie*, 559 F.2d 618, 620, 195 U.S.P.Q. 6, 8-9 (C.C.P.A. 1977) (optimization of a parameter not recognized as a result-effective variable is an exception to the rule that “discovery of an optimum value of a variable in a known process is normally obvious”). Thus, the Office’s proffered rationale of routine optimization by lengthening h53AON1 does not apply.

Given the length of 16-50 bases and the many possible variations in nucleobase and backbone chemistry taught by van Ommen et al., there is *not* a “finite number” of known, predictable solutions to modifying h53AON1 such that one of ordinary skill in the art would arrive at the claimed morpholino antisense oligonucleotides of 20 to 31 bases having a base sequence 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69), and having at least 12 consecutive bases of SEQ ID NO: 195 in which uracil bases are thymine bases, with a reasonable expectation of success. In fact, there is

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absolutely nothing in van Ommen et al. about selecting a morpholino chemistry backbone and thymine bases, rather than uracil bases.

iii. High level of unpredictability in the field with no reasonable expectation of success

Even assuming, *arguendo*, that one of ordinary skill would have selected h53AON1 of van Ommen et al. as a lead compound and would have been motivated to modify it in the particular way necessary to arrive at the subject matter of the claims, there would be no reasonable expectation of success because at the time the instant invention was made, there was a significant level of unpredictability associated with selecting specific antisense oligonucleotide sequences to induce effective dystrophin exon skipping. For example, the specification as originally filed notes that the size or length of an antisense oligonucleotide is not predictive of its efficacy (specification at page 21, lines 11-12). In addition, Applicants have found that there is no standard motif that can be blocked or masked by antisense molecules to redirect splicing (specification at page 21, lines 18-20). Applicants submit that the cited art does not provide sufficient guidance to arrive at the claimed subject matter considering the high level of unpredictability in the art.

Applicants refer the Office to van Deutekom *et al.* (2003) Nature Reviews, 4:774-783 (“van Deutekom Review”; submitted in an Information Disclosure Statement on September 22, 2017). This article is a review that generally discloses exon skipping in the dystrophin gene. The van Deutekom Review notes that interfering with exon selection for inclusion before splicing is “a process that is *not yet well understood*” (page 780, col. 1, lines 1-3, emphasis added).

Applicants also refer the Office to U.S. Patent Application Publication No. 2006/0147952 to van Ommen et al. (the ‘952 Publication) describe an approach in which “AONs were *empirically analyzed* for the induction of exon skipping.” (‘952 Publication at [0051]; emphasis added.) Such an approach relies on experience or observation and provides no indication as to what parameters are critical for the design of exon skipping antisense. As each antisense oligonucleotide must be empirically analyzed, the results are *unpredictable* as reported in Table 2 of the ‘952 Publication:

[t]heir different lengths and G/C contents (%) *did not correlate to their effectivity in exon skipping* (1, induced skipping, 2, no skipping). The AONs were directed to purine

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(A/G)-rich sequences as indicated by their (antisense) U/C content (%). Skipping of the target exons resulted in either an in-frame (IF) or out-of-frame (OF) transcript. (van Ommen et al. [0153], Table 2, footnote *a*; emphasis added.)

Additional evidence of unpredictability is found by analyzing the antisense sequences in Table 2 of the ‘952 Publication. For example, the two antisense oligonucleotides designed to induce skipping of exon 2 have overlapping nucleotide sequences:

h2AON1	cccauuuugugaauguuuucuuuu
h2AON2	uugugcauuuacccaauuugug

Despite the overlap in sequence, h2AON1 purportedly induced skipping, while h2AON2 did *not*. (‘952 Publication at Table 2.) And yet for another pair of overlapping AONs, both members of the pair did purportedly induce skipping:

h29AON1	uauccucugaaugucgcauc
h29AON2	gguauccucugaaugucgc

There is no explanation in the ‘952 Publication for these disparate results.

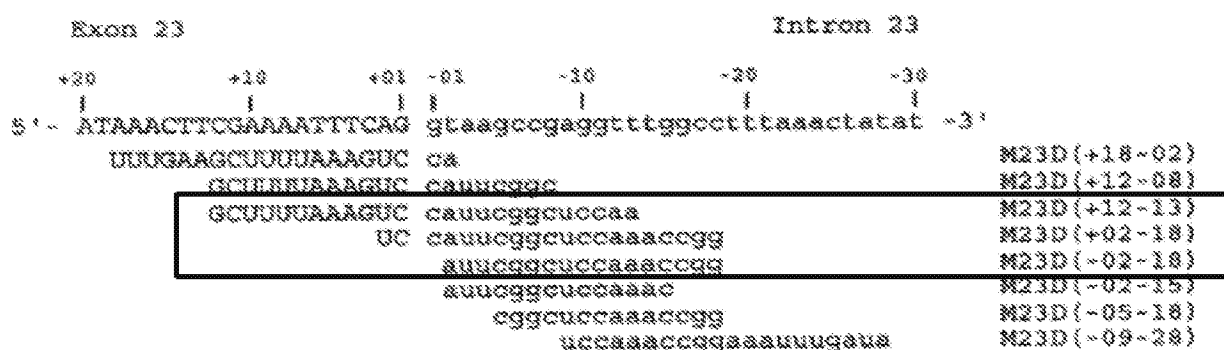
Much of the data in Table 2 of the ‘952 Publication was published in 2002 by Aartsma-Rus et al. (Neuromuscular Disorders, 12:S71-S77 (2002) (“Aartsma-Rus (2002)”); submitted in an Information Disclosure Statement on September 22, 2017). Aartsma-Rus (2002) discloses two specific oligonucleotides directed at dystrophin exon 53 and notes that there is *no correlation* between the length or sequence of the oligonucleotide and its effectiveness at inducing exon skipping. (Aartsma-Rus (2002) at page S76, col. 1, lines 43-45.) Still further, Aartsma-Rus (2002) teaches that *significant experimentation is required* to arrive at specific oligonucleotides, noting that “[w]e therefore have *no insight* into the actual position of the targeted sequence within the completely folded RNA structure. Its accessibility, and thus the effectivity of any designed AON, will therefore have to be tested *empirically* in the cells, as was done in this study.” (Aartsma-Rus (2002) at page S76, col. 1, lines 4-6; emphasis added.)

Another study, co-authored by one of the Applicants, examined skipping of exon 23 from the mouse DMD gene by RT-PCR following transfection with a series of overlapping 2’-Me-O-PS AONs, as shown in the following figure. Of the antisense oligonucleotides tested, only M23D(+12-13), M23D(+02-18), and M23D(-02-18) were effective in inducing detectable exon

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skipping. (Mann et al., J. Gene Med., 4(6): 644-654 (2002); submitted in an Information Disclosure Statement on September 22, 2017.)



(Mann et al. at 646.) Notably, the *shorter* antisense oligonucleotide M23D(-02-18), which is only *17 nucleotides* in length, was particularly efficient at inducing skipping and was reported to induce exon skipping at concentrations as low as 5 nM. The authors concluded that they could improve “the efficiency of the technique” by “*reduc[ing] the size* and the effective dose of the AO[N]s” examined. (Mann et al. at 644; emphasis added.)

Similar examples of unpredictability were reported by van Ommen et al. and other investigators at or near the date of Applicants' invention. In a 2005 publication the same design rationale described by van Ommen and coworkers was applied again. (Aartsma-Rus et al. Oligonucleotides, 15(4): 284-297 (2005) ("Aartsma-Rus (2005)"; submitted in an Information Disclosure Statement on September 22, 2017.) Table 1 of Aartsma-Rus (2005) provides the sequences of the antisense oligonucleotides and whether or not they induced skipping. (Aartsma-Rus (2005) at 285, first and second columns.) The following pairs of antisense oligonucleotides are found in the Table (+ and – refer to skipping ability):

h29AON10	guaguucccuccaaccg	-
h29AON11	cauguaguucccucc	+
h43AON2	uuguuaacuuuuucccauu ⁴	+

⁴ There is a discrepancy between the disclosure of Aartsma-Rus (2005) and the sequence as shown by van Ommen et al. In the 2005 publication, the sequence is shown as uuguuaacuuuuucccauu, while in Table 2

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h43AON3	uguuaacuuuuucccauugg	-
h46AON8	gcuuuucuuuuaguugcugc	++
h46AON9	uuaguugcugcucuu	-
h48AON3	ggucuuuuauuugagcuuc	-
h48AON7	uuuauuugagcucaauuu	+

It is evident from these results that applying the design rationale described by van Ommen et al. is a hit-or-miss proposition in terms of whether any given antisense oligonucleotide will be capable of inducing skipping, *even in situations where the antisense oligonucleotides are very similar to each other in terms of nucleotide sequence, and other variables concerning the chemical backbone are fixed*. All of the antisense oligonucleotides described in the study “contain 2’-O-methyl RNA and full-length phosphorothioate (PS) backbones.” (Aartsma-Rus (2005) at 285.) None of the antisense oligonucleotides disclosed were longer than 24 nucleotides, and the majority of the antisense oligonucleotides were 20 nucleotides in length or shorter. (Aartsma-Rus at Table 1.) None of these antisense oligonucleotides include non-natural bases. Given the common chemical modifications of these antisense oligonucleotides, the data reported in this paper demonstrates the unpredictable impact that length and nucleotide composition make with respect to efficiency in inducing exon skipping.

The recognition of the lack of predictability in the field of exon skipping continued beyond 2005. A 2007 paper co-authored by van Ommen co-inventors Aartsma-Rus and van Deutekom states that “several years after the first attempts at dystrophin exon skipping with AOs [antisense oligonucleotides], *there are still no clear rules to guide investigators in their design*, and in mouse and human muscle cells *in vitro there is great variability for different targets and exons*.” (Arechavala-Gomeza et al. Hum. Gene Ther., 18(9): 798-810, 807 (2007); submitted in an Information Disclosure Statement on September 22, 2017; emphasis added.)

And again in 2009 van Ommen and co-workers wrote that while existing software programs can facilitate design, “in general *a trial and error procedure* is still involved to

of van Ommen et al. it shown as above having a sequence of "ccc" toward the 3’ end of the AON. It is assumed the latter is correct as it corresponds to the sequence of h43AON3.

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identify potent AONs.” (Aartsma-Rus et al., *Mol. Ther.*, 17(3):548-553 (2009) at 548; submitted in an Information Disclosure Statement on September 22, 2017; emphasis added.)

Evidence that selecting specific antisense oligonucleotide sequences to induce effective dystrophin exon skipping remains an unpredictable exercise is also found in a 2011 publication by Wu *et al.* (2011) *PLoS One*, 6(5): e19906 (submitted in an Information Disclosure Statement on September 22, 2017). Although Wu *et al.* is evidence developed after the instant filing date, the level of unpredictability in the art directly relates to whether the results obtained with any specific species would be unexpected and courts have held that it is not “improper to conduct additional experiments and provide later-obtained data in support of patent validity.” *Knoll Pharm. Co., Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004). Evidence of the lack of predictability of in the field is relevant to the non-obviousness of the claimed antisense oligonucleotides over the cited art.

Wu *et al.* describe a systematic approach for identifying antisense oligonucleotides of high efficacy in inducing dystrophin exon skipping. Wu *et al.* designed 25 antisense oligonucleotides (AOs) to cover more than two thirds of exon 50 of the human dystrophin gene and the two flanking intron sequences. Wu *et al.* determined the efficiency of AO-induced skipping of exon 50 by comparing the activity of a series of AOs. Table 1 on page 4 of the publication summarizes all the AOs tested, including both 2'-O-methyl phosphorothioate and morpholino antisense oligonucleotides, as well as their reported activity in two assays. The exon skipping effect was determined using both a GFP reporter cell line with GFP expression coupled to exon 50 skipping and normal human myoblasts.

As shown in Table 1, Wu *et al.* tested AOs having a common 5' or 3' termini, but varied in length. Shown below is an excerpt from Table 1 of Wu *et al.*

hES0 AO2PS	-19-1	5'-CUUUAACAGAAAAGCAUAC-3'	19 bp	-	-	N/D
hES0 AO3PS	-19+1	5'-UCUUUAACAGAAAAGCAUAC-3'	20 bp	-	-	N/D
hES0 AO4PS	-19+3	5'-CCUCUUUAACAGAAAAGCAUAC-3'	22 bp	4%	3%	N/D
hES0 AO5PS	-19+8	5'-AACUCCUCUUUAACAGAAAAGCAUAC-3'	27 bp	21%	29%	N/D
hES0 AO6PS	-19+13	5'-CUUCUAACUCCUCUUUAACAGAAAAGCAUAC-3'	32 bp	3%	<1%	N/D

Each of these AOs target exon 50 starting at position (-19) and ending at position (-1), (+1), (+3), (+8) and (+13), respectively, and the oligonucleotides overlap at the 3' end. These AOs varied in length from 19 to 32 bases and the data shows that increasing AO length does not

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necessarily increase exon skipping activity and there is no reasonable expectation of success in increasing AO length to obtain increased exon skipping activity. For example, the 19- and 20-mer AOs hE50 AO2PS and hE50AO3PS were inactive. Increasing the length to 22 and 27 bases (hE50 AO4PS and hE50 AO5PS, respectively) resulted in increased activity, but a further increase to 32 bases (hE50 AO6PS) decreased activity significantly. Specifically, hE50 AO5PS is 5 nucleotides longer than hE50 AO4PS, but the level of GFP of hE50 AO5PS is 17% higher with respect to GFP assay and 26% higher with respect to human myoblasts. hE50 AO5PS is 5 nucleotides shorter than hE50 AO6PS, but the level of GFP of hE50 AO5PS is 18% higher with respect to GFP and 28% higher with respect to human myoblasts.

The data provided in Table 1 also demonstrate that when hE50 AO4PS (-19+3) was extended five nucleotides in length to hE50A AO5PS (-19+8), activity was increased. Notably, however, the addition of yet another five nucleotides to hE50 AO6PS (-19+13) essentially eliminated the activity.

In yet another example, a relatively short oligonucleotide (hE50 AO19PS; +97-5) at the 3' end of the exon showed low activity (3%) with respect to GFP, and activity did not increase when the oligonucleotide was lengthened by five or nine nucleotides at the 5' end (hE50 AO20PS and hE50 AO21PS, respectively) or by five nucleotides in the 3' direction (hE50 AO16PS). These four antisense oligonucleotides showed no activity in the human myoblasts. Thus, Wu *et al.* demonstrate that increasing or decreasing AO length results in unpredictable effects on exon skipping.

Importantly, the Patent Trial and Appeal Board (PTAB) in Interference No. 106,007 (“the ‘007 interference”) concerning exon 53 antisense oligonucleotides for DMD held that the field of antisense oligonucleotides for exon skipping for DMD was unpredictable at the time the instant application was filed. Its decision was based on the foregoing evidence and expert testimony. *See* Decision on Motions in Interference No. 106,007 (exon 53) dated May 12, 2016 (decision final upon withdrawal of CAFC Appeal No. 2016-2262; Decision on Motions previously submitted in an Information Disclosure Statement on September 22, 2017). Specifically, the PTAB determined that sequence length of antisense oligonucleotides that would maintain exon skipping was substantially unpredictable at the time US Application No. 11/233,495 was filed by Academisch Ziekenhuis Leiden (“AZL”). *See id.* at page 5, line 26 to page 6, line 3. Applicants note that the ‘495 application claims priority to the van Ommen *et al.* PCT application presently cited by the Office. In its Decision, the PTAB

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considered the foregoing evidence as representative of the state of the art with Exhibits 2010 and 2015 in Interference 106,007 corresponding to Aartsma-Rus and Wu *et al.*, submitted herewith as Appendices A and C, respectively. Unpredictability in this art was determined by the PTAB to have existed at the time of the instant invention (and years afterwards).

Upon consideration of this evidence, the PTAB stated “[t]he evidence indicates that at the time AZL filed its application, the identification of AONs that will cause exon skipping was generally thought to be unpredictable. One of the significant factors causing that unpredictability is the effect of the number of nucleobases present in the AON.” (Decision on Motions at page 17 (emphasis added)). In particular, the relationship between length of a base sequence and the ability of an antisense oligonucleotide to induce exon skipping was considered by the PTAB.

Despite the unpredictability in the art, the PTAB found obvious a 20mer AON based on SEQ ID NO: 193 over a completely overlapping 18mer (h53AON1). In this particular circumstance, the PTAB found that “a degree of exon skipping capability would likely be maintained due to a change in a *small number of complementary nucleobases* of an AON known to cause skipping” and, therefore, concluded “[i]t would have been obvious, for example, to add the *two* complementary nucleobases dictated by the known sequence of exon 53 to either end of h53AON1 with a reasonable expectation that the resultant 20 base AON would cause exon skipping.” *Id.* at pages 41-42 (emphasis added).

In contrast to the narrow issue considered by the PTAB described above, the PTAB does not support a determination of obviousness of the instant claims. The PTAB’s determination of unpredictability still applies. And to arrive at the instantly claimed antisense oligonucleotides, a person of ordinary skill would have to modify h53AON1 by adding at least *9 bases* (and would have to do so with a reasonable expectation of success). Such a modification in length cannot be said to be predictable under the Decision in the ‘007 interference. Accordingly, it would not have been obvious to extend h53AON1 by 9 bases at least because of the highly degree of unpredictability discussed above, and the Office failed to provide evidence to the contrary.

Furthermore, similar to the Office’s assertion, AZL argued that upon identification of h53AON1, “one skilled in the art would have investigated extended complementary sequences with the expectation that the longer sequences would bind and cause skipping.” *Id.* The PTAB did not find this argument persuasive at least because AZL failed to provide any

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evidence to support the basis for this expectation. *Id.* at page 18. Like AZL, the Office failed to provide evidence to support this argument. *See* Office Action at page 5. Accordingly, Applicants urge the Office to adopt the PTAB's determination of unpredictability in the field of exon skipping for DMD.

In summary, the van Deutekom Review, Aartsma-Rus and Wu *et al.* references, along with the Decision on Motions in the '007 interference, serve to illustrate the unpredictability associated with selecting *specific* antisense oligonucleotides that are effective for inducing skipping of dystrophin exons. Accordingly, the Office failed to establish a *prima facie* case of obviousness with respect to the predictability of the outcome in combining teachings of van Ommen *et al.* and Koenig *et al.* in the manner proposed to arrive at the claimed invention.

In view of the preceding remarks, Applicants submit that the Office failed to establish a *prima facie* case of obviousness based on the cited art. As such, Applicants respectfully request reconsideration and withdrawal of this obviousness rejection.

Double Patenting

Claims 2 and 3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 8,455,636. Applicants respectfully traverse this rejection.

The Office asserts "the instant claims and the claims of the patent are drawn to antisense oligonucleotides having at least 17 consecutive bases of SEQ ID No. 193." Office Action at page 6. However, Applicants note the instant claims are drawn to antisense oligonucleotide having 20-31 bases and comprising at least 12 consecutive bases of SEQ ID NO: 195. Moreover, the '636 patent is directed to an antisense oligonucleotide comprising 20-50 bases and at least 20 consecutive bases of SEQ ID NO: 193. As such, Applicants point out that there is only a 2 base overlap between SEQ ID NOs: 193 of the '636 Patent and SEQ ID NO: 195 of the instant claims. Accordingly, Applicants respectfully request that the Office consider withdrawing the instant rejection in view of these facts and the foregoing remarks.

Claims 2 and 3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 8,232,384. Applicants respectfully request clarification of this rejection. Specifically, The Office asserts

Application No.: 15/705,172

Docket No.: AVN-008CN41

“the instant claims and the claims of the patent are drawn to antisense oligonucleotides having at least 17 consecutive bases of SEQ ID No. 193.” Office Action at page 7. However, Applicants note the instant claims are drawn to antisense oligonucleotide having 21-30 bases and comprising at least 12 consecutive bases of SEQ ID NO: 195. Moreover, the ‘384 patent is directed to an antisense oligonucleotide *consisting* of SEQ ID NO: 195. Accordingly, Applicants respectfully request clarification.

Application No.: 15/705,172

Docket No.: AVN-008CN41

CONCLUSION

In view of the foregoing, Applicants respectfully submit that the pending claims are in condition for allowance. If a telephone conversation with Applicants' attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 217-4626. If a fee is due with this submission, please charge our Deposit Account No. 12-0080 under Order No. AVN-008CN41, from which the undersigned is authorized to draw

Dated: January 5, 2018

Respectfully submitted,
Electronic signature: /Amy E. Mandragouras,
Esq./
Amy E. Mandragouras, Esq.
Registration No.: 36,207
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4626
(617) 217-4699 (Fax)
Attorney/Agent For Applicant

Electronic Acknowledgement Receipt

EFS ID:	31418918
Application Number:	15705172
International Application Number:	
Confirmation Number:	2879
Title of Invention:	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF
First Named Inventor/Applicant Name:	Stephen Donald WILTON
Customer Number:	123147
Filer:	Amy E. Mandragouras
Filer Authorized By:	
Attorney Docket Number:	AVN-008CN41
Receipt Date:	05-JAN-2018
Filing Date:	14-SEP-2017
Time Stamp:	16:01:20
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment/Req. Reconsideration-After Non-Final Reject	2018_01_05_Response_to_Office_Action_AVN-008CN41.pdf	947608 e3375c8063d69fd5d3ec803dd094e542d6c09b18	no	19

Warnings:

Information:

Total Files Size (in bytes):

947608

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc code: IDS

36996

PTO/SB/08a (03-15)

Doc description: Information Disclosure Statement (IDS) Filed

Approved for use through 07/31/2016. OMB 0651-0031

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		15705172
	Filing Date		2017-09-14
	First Named Inventor		Stephen Donald WILTON
	Art Unit		1674
	Examiner Name	K. Chong	
	Attorney Docket Number		AVN-008CN41

U.S.PATENTS							Remove
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	
	1	9758783		2017-09-12	Wilton et al.		
If you wish to add additional U.S. Patent citation information please click the Add button.							Add
U.S.PATENT APPLICATION PUBLICATIONS							Remove
Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	
	1	20110046203	A1	2011-02-24	Wilton et al.		
	2	20170283799	A1	2017-10-05	KAYE		
	3	20170292125	A1	2017-10-12	SAZANI et al.		
	4	20170369875	A1	2017-12-28	BESTWICK et al.		
	5	20170369876	A1	2017-12-28	BESTWICK et al.		

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number # 36997	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	K. Chong
Attorney Docket Number	AVN-008CN41

6	20180002689	A1	2018-01-04	BESTWICK et al.
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If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ² i	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T ⁵
	1							

If you wish to add additional Foreign Patent Document citation information please click the Add button.

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
	1	European Decision of the Opposition Division, European Application No. 10004274.6, dated December 19, 2017, 23 pages.	
	2	Extended European Search Report, EP 16172354.9, dated January 23, 2017, 7 pages.	
	3	Extended European Search Report, EP 17159328.8, dated September 5, 2017, 10 pages.	
	4	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Filing Priority Statement, 2 pages, Patent Interference No. 106,007, dated November 18, 2014 (Doc 215)	

If you wish to add additional non-patent literature document citation information please click the Add button.

EXAMINER SIGNATURE

Examiner Signature		Date Considered	
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	K. Chong
Attorney Docket Number	AVN-008CN41

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number # 36999	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	K. Chong
Attorney Docket Number	AVN-008CN41

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

- ☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.
- ☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Amy E. Mandragouras, Esq./	Date (YYYY-MM-DD)	2018-01-05
Name/Print	Amy E. Mandragouras, Esq.	Registration Number	36,207

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: January 5, 2018
Electronic Signature for Amy E. Mandragouras, Esq.: /Amy E. Mandragouras, Esq./

Docket No.: AVN-008CN41
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Stephen Donald Wilton *et al.*

Application No.: 15/705,172

Confirmation No.: 2879

Filed: September 14, 2017

Art Unit: 1674

For: ANTISENSE OLIGONUCLEOTIDES FOR
INDUCING EXON SKIPPING AND
METHODS OF USE THEREOF

Examiner: K. Chong

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (SIDS)

Dear Sir:

In compliance with 37 C.F.R. § 1.56, 1.97 and 1.98, the attention of the U.S. Patent and Trademark Office is hereby directed to the documents listed on the attached PTO/SB/08. In accordance with 37 C.F.R. § 1.98(a)(2)(i)-(iv), Applicant submits herewith copies of the non-patent literature references, but has not included copies of U.S. patents and/or U.S. patent applications.

It is respectfully requested that the documents listed on the PTO/SB/08 be expressly considered by the Examiner during the prosecution of this application, and that the documents be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

Application No.: 15/705,172 (Information Disclosure Statement)

Docket No.: AVN-008CN41

Applicant calls to the attention of the Examiner the following Applications and provides copies of Office Actions cited therein, as well as, copies of Office Actions from Applications previously made of record:

Applications				
<i>Examiner's Initials</i>	<i>Serial No.</i>	<i>Filing Date</i>	<i>First Named Inventor</i>	<i>Docket No.</i>
	15/349,778	11-11-2016	Peter SAZANI	AVN-009DVCN6
	15/420,823	01-31-2017	R.K. BESTWICK	AVN-010PCCN2
	15/359,152	11-22-2016	E.M. KAYE	AVN-012ACN
	15/422,127	February 1, 2017	R.K. BESTWICK	AVN-013BCN
	15/417,401	01-27-2017	R.K. BESTWICK	AVN-017CN

Office Actions (copies enclosed)			
<i>Examiner's Initials</i>	<i>Serial No.</i>	<i>Date Mailed from USPTO</i>	<i>Examiner</i>
	15/422,127	November 27, 2017	D.H. Shin
	15/417,401	October 12, 2017	D.H. Shin
	15/359,152	January 5, 2018	E. Poliakova-Georgan
	15/420,823	November 2, 2017	A. Hudson Bowman
	14/776,533	November 16, 2017	D. Shin

The Examiner is requested to review the file histories of these applications, including cited references, Office Actions, Responses, etc., and is asked to contact Applicant's Attorney if the Examiner would like the Applicant to supply copies of any or all of the information included in any of these applications. For any of these applications, if Applicant's Attorney is not contacted by the Examiner with such a request, then it will be concluded that the Examiner has reviewed or will review the file content of these applications.

Applicant respectfully requests that the Examiner initial the blank columns next to the cited Applications and Office Actions, to indicate that the information has been considered by the Examiner. Alternatively, Applicant requests that the Examiner insert the phrase, "All references considered except where lined through," on each page of the Information Disclosure Statement, along with the Examiner's initials.

Application No.: 15/705,172 (Information Disclosure Statement)

Docket No.: AVN-008CN41

The filing of this Information Disclosure Statement is not to be interpreted as a representation that the cited documents are material, that an exhaustive search has been conducted, or that no other relevant information exists. Nor shall the citation of any documents herein be construed *per se* as a representation that such document is prior art. Moreover, Applicant understands the Examiner will make an independent evaluation of the cited documents.

This Information Disclosure Statement is filed after the mailing date of a first Office Action on the merits, but before the mailing date of any of a Final Action under 37 C.F.R. § 1.113, a Notice of Allowance under 37 C.F.R. § 1.311 or an action that otherwise closes prosecution in this application (37 C.F.R. § 1.97(c)).

Please charge our Deposit Account No. 12-0080 in the amount of \$90.00 covering the fee set forth in 37 C.F.R. § 1.17(p). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 12-0080, under Order No. AVN-008CN41.

Dated: January 5, 2018

Respectfully submitted,

Electronic signature: /Amy E. Mandragouras, Esq./
Amy E. Mandragouras, Esq.
Registration No.: 36,207
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4626
(617) 217-4699 (Fax)
Attorney/Agent For Applicant

Electronic Patent Application Fee Transmittal				
Application Number:		15705172		
Filing Date:		14-Sep-2017		
Title of Invention:		ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF		
First Named Inventor/Applicant Name:		Stephen Donald WILTON		
Filer:		Amy E. Mandragouras		
Attorney Docket Number:		AVN-008CN41		
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	2806	1	90	90
Total in USD (\$)				90

Electronic Acknowledgement Receipt

EFS ID:	31418840
Application Number:	15705172
International Application Number:	
Confirmation Number:	2879
Title of Invention:	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF
First Named Inventor/Applicant Name:	Stephen Donald WILTON
Customer Number:	123147
Filer:	Amy E. Mandragouras/Anita Costa
Filer Authorized By:	Amy E. Mandragouras
Attorney Docket Number:	AVN-008CN41
Receipt Date:	05-JAN-2018
Filing Date:	14-SEP-2017
Time Stamp:	16:34:08
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$ 90
RAM confirmation Number	010818INTEFSW00003620120080
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	EPO_Comm_Decsion_from_OD_dated_19_Dec_2017.PDF	1601222	no	23
			c83843dd51298fe3a40cb40bda5ae36c43624a3b		
Warnings:					
Information:					
2	Non Patent Literature	EESR_AVN_009EPDV2.pdf	202097	no	7
			cfe1d6db14b304495624a8d9c867c6165f4e8754		
Warnings:					
Information:					
3	Non Patent Literature	EESR_008EPDV5.PDF	318700	no	10
			626dd3b5b8841ce22bb9922016be0c3684ac2477		
Warnings:					
Information:					
4	Non Patent Literature	106007_DOC215.pdf	31278	no	2
			a85666f914d6bdc9f402afc21b8dbec1fce15822		
Warnings:					
Information:					
5	Other Reference-Patent/App/Search documents	14776533_02.pdf	746034	no	24
			0f37cd3fbf4e8bacf801363122b0e4cb4d33be9f		
Warnings:					
Information:					
6	Other Reference-Patent/App/Search documents	15359152.pdf	228974	no	9
			f2776441936bb0162cd66ed709480c568f0cc304		
Warnings:					
Information:					

7	Other Reference-Patent/App/Search documents	15417401.pdf	359713 0dcff7a1d291f8d7459f13ac48cf05141e494e84	no	13
Warnings:					
Information:					
8	Other Reference-Patent/App/Search documents	15420823.pdf	202848 d54128e633ebb97e95c3be278715d057303c0400	no	8
Warnings:					
Information:					
9	Other Reference-Patent/App/Search documents	15422127.pdf	396508 96dded42e5f92fc1ffb473a51e6f21e71b03928e	no	15
Warnings:					
Information:					
10	Information Disclosure Statement (IDS) Form (SB08)	SB08_02.pdf	1059785 052e694073ccf52738f55bd75a0d013df2f70ec0	no	5
Warnings:					
Information:					
11	Information Disclosure Statement (IDS) Form (SB08)	IDSTRANS.pdf	33954 6db9b3bfe64371a046336d29cee5697246798181	no	3
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
12	Fee Worksheet (SB06)	fee-info.pdf	30688 5106089018ed7706631a6ead29940f834ac57004	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			5211801		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

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National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



DEADLINE: Due Date Registered
REVIEW: # 37010

ACTION: Opposition Decision

ATTORNEY: AAW

Added by Louise Ryder @ 12:04 pm, Dec 21, 2017

European Patent Office
Postbus 5818
2280 HV Rijswijk
NETHERLANDS
Tel: +31 70 340 2040
Fax: +31 70 340 3016



Deadline Checked

By Lisa Stuart
1:40 pm, Dec 21, 2017

Formalities Officer
Name: Masserut, Marijo
Tel: +31 70 340 - 8961
or call
+31 (0)70 340 45 00

D Young & Co LLP
120 Holborn
London EC1N 2DY
ROYAUME-UNI

Application No. / Patent No. 10 004 274.6 - 1401 / 2 206 781 /	Ref. X109014EPA AAW	Date 19.12.2017
Proprietor THE UNIVERSITY OF WESTERN AUSTRALIA		

Decision revoking the European Patent (Art. 101(2) and 101(3)(b) EPC)

The Opposition Division - at the oral proceedings dated 30.11.2017 - has decided:

European Patent No. EP-B- 2 206 781 is revoked.

The reasons for the decision are enclosed.

Possibility of appeal

This decision is open to appeal. Attention is drawn to the attached text of Articles 106 to 108 and Rules 97 to 98 EPC.

Opposition Division:

Date 19.12.2017

Sheet 2

Application No.: 10 004 274.6

Chairman:
2nd Examiner:
1st Examiner:

Macchia, Giovanni
Romano, Alper
Bucka, Alexander



Masserut, Marilú
Formalities Officer

Tel. No.: +31 70 340-8961

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Enclosure(s): 12 page(s) reasons for the decision (Form 2916)
Wording of Articles 106 - 108 and Rules 97-98 EPC (Form 2019)
Minutes of oral proceedings
Annex A (cited documents)

to EPO postal service: 12.12.17

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Sheet 1
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Anmelde-Nr:
Application No: 10 004 274.6
Demande n°:

This decision is based on the following patent documents:

Main Request

Description, Paragraphs

1-106 of the patent specification

Sequence listings, SEQ ID NO

1-212 of the patent specification

Claims, Numbers

1-9 of the patent specification

Drawings, Figures

1-3 of the patent specification

Auxiliary Request 1

idem, but

Claims, Numbers

1-7 filed in electronic form on 22-02-2017

Auxiliary Request 2

idem, but

Claims, Numbers

1-9 filed in electronic form on 22-02-2017

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Auxiliary Request 3

idem, but

Claims, Numbers

1-9 filed in electronic form on 22-02-2017

Auxiliary Request 4

idem, but

Claims, Numbers

1-7 filed in electronic form on 22-02-2017

Auxiliary Request 5

idem, but

Claims, Numbers

1-7 filed in electronic form on 22-02-2017

1 Facts and Submissions

- 1.1 The European patent EP 2 206 781 B1, Application number 10 004 274.6, entitled "Antisense oligonucleotides for inducing exon skipping and methods of use thereof" (hereinafter: the patent) was granted on 2 December 2015 with 9 claims for the designated Contracting States AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK and TR. THE UNIVERSITY OF WESTERN AUSTRALIA, Crawley, Western Australia (AU) is the Proprietor.

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- 1.2 An opposition was filed with the letter of 25 August 2016. The Opponent, Nippon Shinyaku Co., Ltd. (JP), represented by Günter Keller of Lederer & Keller (DE), opposed the patent EP 2 206 781 B1 in its whole extent under Article 100(a) EPC in conjunction with Article 56 EPC, Article 100(b) EPC and Article 100(c) EPC.
- 1.3 In response to the opposition, the Proprietor, represented by Aylsa Williams and Garreth Duncan of D. Young & Co. (UK), filed arguments and 5 auxiliary requests with the submission dated 22 February 2017. The Proprietor requested the rejection of the opposition, i. e. the maintenance of the patent as granted, or alternatively the maintenance on the basis of any of the auxiliary requests 1 to 5.
- 1.4 Both parties requested oral proceedings. Therefore, oral proceedings were appointed for 30 November 2017.
- 1.5 The Opponent replied to the summons to oral proceedings with the letter dated 29 September 2017, *inter alia* submitting further experimental data designated as D8-1 and D13 (subsequently renumbered as D16).
- 1.6 The Proprietor replied with the submissions dated 29 September 2017 with further comments and three additional documents D13 to D15.
- 1.7 Oral proceedings took place on 30 November 2017.
- 1.8 D1 to D8 have been submitted by the Opponent with the notice of opposition of 25 August 2016, whereas the Proprietor filed D9 to D12 with the reply dated 22 February 2017. D13 to D15 have been submitted by the Proprietor with the letter dated 29 September 2017. D8-1 and D16 (filed as D13, renumbered) have been submitted by the Opponent with the reply to the summons dated 29 September 2017. A list of the cited documents is attached as Annex A.

Reasons for the Decision

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- 2 The opposition is admissible, since it fulfils the requirements of Article 99(1) and Rule 76 EPC.

Main Request

Claim 1 of the main request, i. e. claim 1 as granted, reads as follows:

"1. An isolated antisense oligonucleotide that binds to human dystrophin pre-mRNA, wherein said oligonucleotide is 20 to 31 nucleotides in length and is an oligonucleotide that is specifically hybridizable to an exon 53 target region of the Dystrophin gene designated as annealing site H53A (+23+47), annealing site H53A (+39+69), or both, wherein said antisense oligonucleotide is a morpholino antisense oligonucleotide, and, wherein said oligonucleotide induces exon 53 skipping."

3 Article 100(c) EPC

- 3.1 The Opponent argued that the amendments of claim 1 as granted would not be allowable in view of the requirements of Article 123(2) EPC and Art. 76(1) EPC, since the patent is derived from a divisional application of an earlier application. *Inter alia*, (i) the intermediate generalisation in claim 1, referring to the binding of the oligonucleotides to annealing sites H53A(+23+47), H53A(+39+69) or to *both* sites was objected to. Further objections were raised concerning (ii) the "specifically hybridizable" feature, (iii) the "morpholino" oligonucleotides, (iv) the length of "20 to 31 nucleotides", (v) the "exon skipping" requirement and (vi) the selection of these features from at least two lists.
- 3.2 The Proprietor indicated the basis for the amendments of the claims as granted and argued that the amendments were allowable. It was submitted that the "morpholino" feature was not inextricably linked to the oligonucleotides in table 1A and that the general part of the application as filed disclosed the use of oligonucleotides, in which both the sugars and the internucleoside linkage are replaced (cf. page 26 of the earlier application as filed, WO2006/000057). The length of 20 to 31 was mentioned as a preferred length on page 21, lines 12-15. "Specifically hybridizable" was disclosed on page 23, last paragraph. The range (+23 to +69) of the region to be targeted could be derived clearly from page 62 and table 39.

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- 3.3 The Opposition Division came to the conclusion that the originally filed application does not provide a valid basis for the features of (i) targeting both H53A(+23+47) and H53A(+39+69), (iii) the "morpholino" and (iv) the length of 20 to 31 nucleotides mentioned in claim 1. Inevitably, (vi) the combination of these features is not supported by the earlier application as filed.
- 3.3.1 The mere reference to overlapping oligonucleotides (page 36, lines 19-20 of the application as filed) does not directly and unambiguously disclose oligonucleotides binding to (i) both of the two specific sites mentioned in claim 1.

The fact that some of the exemplified oligonucleotides (page 62 of the application as filed) bind to partially overlapping regions, but apparently never to the entire region +23+69, likewise does not provide a sufficient teaching for the proposed amendment. The +23+47 oligonucleotide in table 39 induces "very faint skipping to 50 nm", whereas the +39+69 oligonucleotide induces "strong skipping to 50 nm". Hence, based on table 39, the skilled person would not conclude that any oligonucleotide binding to both sites H53A(+23+47), i. e. showing very faint skipping, and H53A(+39+69), showing strong skipping, is encompassed by the teaching of the application as filed. The table on page 62 also refers to an additional oligonucleotide designated H53A(+150+176) that induces the same level of "very faint skipping to 50 nm". However, neither the combination of the +39+69 oligonucleotide with the +23+47 oligonucleotide nor with the +150+176 oligonucleotide is disclosed on page 62. Page 62, lines 7-11, refers to a combination of different oligonucleotides in a "cocktail" of three oligonucleotides, but the target sites of this combination (+23+47, +150+175 and +14-07) are different from those recited in claim 1.

During the oral proceedings the Proprietor argued that the range +23 to +69 could be derived from the specific points disclosed in the examples (cf. page 62). Reference was made to T201/83. In the case underlying T201/83 a large range (100-900 ppm) was limited to a more narrow range of 690-900 ppm based on a composition with 690 ppm disclosed in one of the examples. In the present case, it is not apparent, where a wider, more generic range has been disclosed, which then has been defined more narrowly (i. e. as +23 to +69). In addition, the claim does not refer to a range of +23 to +69, but refers to the binding of the oligonucleotide to two distinct, albeit slightly overlapping ranges (+23+47 and +39+69). Thus, an oligonucleotide binding to two regions is claimed, as opposed to an oligonucleotide binding to one site somewhere between positions +23 and +69.

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Page 6, lines 14 to 19, was furthermore mentioned. This passage discusses the "joining of two or more antisense oligonucleotide molecules", a concept termed "weasel". However, the joining of two or more oligonucleotides is different from the concept of using a single oligonucleotide targeting two annealing sites. The exemplified "weasels" (cf. table 1C, pages 17-18) target different regions and furthermore all of them fall outside the specified length of 20 to 31 nucleotides.

The Proprietor furthermore referred to T667/08, which emphasized that the "*content (description, claims and drawings)*" of an application should be "*considered in its entirety*" and that literal support is not required. The Board also "*stressed that the Board does not question the principle according to which embodiments of an invention can normally not be freely combined under Article 123(2) EPC but merely emphasises that each embodiment in a disclosure must be construed with the knowledge and understanding aptitude of the skilled person in the art in the light of the whole application*". However, in the present case, the application as filed in its entirety does not disclose - directly and unambiguously- an oligonucleotide binding to the two annealing sites recited in claim 1. The "weasels" disclosed in the application target two sites, but not the ones recited in claim 1 and the concept of a weasel (joining two or more oligonucleotides) does not seem to be compatible with the size limitation (20 to 31) mentioned in claim 1.

- 3.3.2 Page 17, line 3, of the application as filed was mentioned as a basis for (iii) the morpholino feature. This passage is the legend to table 1A ("*With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as 'T'*") and hence seems to apply only to the specific sequences recited in this table. This sentence, which is the only passage mentioning morpholinos in the entire application as filed, does not provide a direct and unambiguous disclosure of morpholino oligonucleotides in general. The Applicant has referred to T714/00 that states that "extracting an isolated feature from an originally disclosed combination and using it for delimiting claimed subject-matter can only be allowable under the concept of Article 123(2) EPC if that feature is not inextricably linked with further features of that combination". In the present case, it is apparent from the position of the sole reference to morpholinos, i. e. its mentioning in the legend to table 1A, that it is inextricably, structurally and functionally, linked to the oligonucleotides shown in said table (in T714/00 the proposed amendments were found to contravene the requirements of Article 123(2) EPC; the same conclusion was reached in T1067/97).

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The Proprietor furthermore referred to pages 26 and 27 in the general part of the description, which would disclose the combination of both sugar and backbone replacements, independent of any sequences. Particular reference was made to page 26, lines 27-30, that states that in "other preferred oligonucleotide mimetics, both the sugar and the inter-nucleoside linkage, i. e., the backbone, of the nucleotide units are replaced with novel groups". Morpholinos were known to the skilled person and it was understood that in morpholinos both the ribose and the internucleoside linkage are replaced (cf. letter of the Proprietor dated 29 September 2017, page 3). However, neither this passage on page 26 nor page 27 refers to morpholinos. Morpholinos are also not the only possibility of replacing both the sugar and the backbone; peptide nucleic acids are explicitly mentioned in the general part of the description (cf. e. g. page 26, line 30 to page 27, line 5).

In addition, page 26, lines 27-30, refers to a replacement "with novel groups", which are not defined. The reference to "novel groups" does not seem to be compatible with the argument that morpholinos were commonly known, i. e. morpholinos could not be regarded as "novel groups".

Thus, in summary, the application as originally filed, when considered in its entirety, does not provide a direct and unambiguous disclosure for morpholino oligonucleotides in the context of present claim 1. The amendments of claim 1 confront the skilled person with new technical information not directly derivable from the application as filed.

- 3.3.3 While the precise meaning of the term "morpholino" is not decisive for the assessment of the requirements of Article 76(1) EPC in the present case, it is noted that the Proprietor seemed to imply (cf. letter of the Proprietor dated 29 September 2017, passage bridging pages 3 and 4) that morpholino AONs have both a morpholino ring and a phosphorodiamidate linkage (referring to D15, figure 2). For the sake of completeness, it is noted that, at least according to D15, figure 4, the intersubunit linkages of morpholinos are not limited to phosphorodiamidate linkages.
- 3.3.4 The (iv) length of 20 to 31 nucleotides is mentioned on page 21, lines 12 to 15. The whole passage reads: "Designing antisense molecules to completely mask consensus splice sites may not necessarily generate any skipping of the targeted exon. Furthermore, the inventors have discovered that size or length of the antisense oligonucleotide itself is not always a primary factor when designing antisense molecules. With some targets such as exon 19, antisense oligonucleotides as short as 12 bases were able to induce exon skipping, albeit not as efficiently as longer (20-31 bases) oligonucleotides. In

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some other targets, such as murine dystrophin exon 23, antisense oligonucleotides only 17 residues long were able to induce more efficient skipping than another overlapping compound of 25 nucleotides." The Proprietor has submitted that the range of 20 to 31 nucleotides was disclosed as preferred embodiment. However, the fact that oligonucleotides of 20 to 31 nucleotides are efficient (and hence preferred) is disclosed in this passage only in respect of oligonucleotides targeting exon 19, but not in respect of oligonucleotides targeting exon 53. The entire passage also makes it clear that it is in fact not predictable, which oligonucleotides would provide the most efficient skipping. In one example (exon 19) it is "longer (20-31 bases) oligonucleotides", in another one (mouse exon 23) "antisense oligonucleotides only 17 residues long were able to induce more efficient skipping than another overlapping compound of 25 nucleotides". Thus, on the one hand, the passage on page 21 is entirely silent about oligonucleotides targeting exon 53. On the other hand, it teaches the skilled person that it is entirely unpredictable, whether longer (20-31 bases) oligonucleotides or shorter oligonucleotides (e. g. 17 residues long) would be more efficient and therefore preferred. For these reasons, the passage on page 21 does not provide a direct and unambiguous basis for the reference to oligonucleotides of 20 to 31 nucleotides length that target annealing sites in exon 53.

- 3.3.5 As far as the combinations of features or the selection from lists are concerned, it follows from the foregoing discussion of e. g. the "morpholino" feature that there is no basis for a combination of said feature with any given oligonucleotide targeting the two sites recited in claim 1 or with the particular length of the oligonucleotide.
- 3.3.6 For these reasons, the Opposition Division arrived at the conclusion that the main request extends beyond the disclosure of the earlier application as originally filed (Article 76(1) EPC).
- 3.3.7 For completeness, it is noted that (v) the functionality of the oligonucleotides to induce exon skipping is repeatedly mentioned in the general part of the disclosure (cf. e. g. pages 5, 20, of the application as filed).
- 3.3.8 The term "specifically hybridizable" (ii) is clearly described on page 23 of the application as filed. This passage provides sufficient basis for this feature of claim 1.

4 Auxiliary Requests 1 to 5

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- 4.1 The auxiliary requests 1 to 5 all suffer from some of the same deficiencies as the main request, since all of these request contain the references to the morpholino oligonucleotide and to the length of 20 to 31 nucleotides. The findings for the amendments of claim 1 of the main request (cf. paragraphs 3.3.2 and 3.3.4, *supra*) apply *mutatis mutandis* to the corresponding amendments of claim 1 of the auxiliary requests 1 to 5.
- 4.2 The conclusions for the amendments of claim 1 of the main request in respect of the targeting of both sites H53A(+23+47) and H53A(+39+69) apply *mutatis mutandis* to the corresponding amendments of claim 1 of auxiliary request 1 (cf. paragraph 3.3.1, *supra*).
- 4.3 Therefore, the auxiliary requests 1 to 5 likewise extend beyond the content of earlier application as originally filed (Article 76(1) EPC).

5 Decision

- 5.1 **Since the ground of opposition according to Article 100(c) EPC prejudices the maintenance of the patent as granted or its maintenance in amended form based on any one of auxiliary requests 1 to 5, the patent is revoked pursuant to Articles 101(2) and 101(3)(b) EPC.**

- 6 While the grounds for opposition referred to in Article 100(a) and (b) EPC were not discussed in the oral proceedings, the Opposition Division wishes to make some comments (*obiter dictum*) concerning the requirements of Article 56 EPC that are valid for the requests currently on file.

It is emphasized that the following comments only reflect the *opinion* of the Opposition Division.

- 6.1 Article 56 EPC
- 6.1.1 The Opponent argued that the subject matter of the present claims would not be inventive in view of the disclosure of documents D3 in combination with D1 or in view of the combination of the teaching of D3 and D4.
- 6.1.2 The Proprietor submitted that document D3 would only teach shorter non-PMO oligonucleotides and that nothing in D3 would indicate a region suitable for longer oligonucleotides resulting in highly efficient skipping. D1 was only dealing with the use of PMOs as tools in investigating vertebrate development

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and hence was from a completely different technical field. The combination of D3 and D4 would likewise not lead the skilled person to the claimed invention, since both documents would only teach 18-mers. It was furthermore argued that the "limited data of the prior art does not make the specific longer PMOs claimed" in the patent obvious.

- 6.1.3 The inventive step is usually assessed by applying the "problem and solution approach". According to the Case Law of the Boards of Appeal of the EPO, 8th edition, 2016, this "consists essentially of (a) identifying the "closest prior art", (b) assessing the technical results (or effects) achieved by the claimed invention when compared with the "closest state of the art" established, (c) defining the technical problem to be solved as the object of the invention to achieve these results, and (d) examining whether or not a skilled person, having regard to the state of the art within the meaning of Art. 54(2) EPC, would have suggested the claimed technical features in order to obtain the results achieved by the claimed invention".
- 6.1.4 Claim 1 of the main request relates to a morpholino antisense oligonucleotide that binds to human dystrophin pre-mRNA, wherein said oligonucleotide is 20 to 31 nucleotides in length and is an oligonucleotide that is specifically hybridizable to an exon 53 target region of the Dystrophin gene designated as annealing site H53A (+23+47), annealing site H53A (+39+69), or both, and wherein said oligonucleotide induces exon 53 skipping.

In the opinion of the Opposition Division, document D3 could be regarded as the closest prior art. It appears that this assessment could be shared by both the Opponent and the Proprietor.

D3 discloses oligonucleotides targeting the exon 53. The region targeted by the oligonucleotides described in D3 is contained in the region H53A (+39+69). D3 explicitly teaches the use of oligonucleotides of up to 50 nucleotides length and with morpholino backbone (cf. D3, claims 3, 12). It is emphasized that the teaching of a patent document cannot be limited to its examples. Thus, the fact that only 18-mers are exemplified does not mean that the teaching and the enabling disclosure provided by D3 is limited to 18-mers.

The difference between the subject matter of claim 1 and the disclosure of D3 consists in the precise region targeted by the oligonucleotides. It appears that the patent does not describe a single morpholino oligonucleotide falling within the scope of the claims; at most the teaching in respect of morpholinos appears to be limited to specific sequences displayed in table 1A (*supra*). The

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patent furthermore does not compare the 18-mers exemplified in the prior art with the longer oligonucleotides presently claimed. The patent provides some data for 2'-O-methyl phosphorothioate oligonucleotides targeting the same region (cf. table 39). Some of these oligonucleotides only induce "very faint skipping". Thus, in view of the data in the patent, no effect appears to be associated with the structural differences, i. e. with the targeting of a different, longer region.

While the Proprietor has provided D12, which shows a comparison between an 18-mer and oligonucleotides of 24 to 31 nucleotides length, there is no comparison with any oligonucleotide of 20 nucleotides length. Based on the data supplied by the Opponent (cf. D8), the slightly longer oligonucleotides (i. e. the 20-mer or the 21-mer) do not seem to be better than the 18-mer. Thus, it seems impossible to draw any conclusion concerning an effect present over the entire scope of the claims. The Proprietor asserted that 20-mer according to claim 1 are more efficient than the prior art oligonucleotides. However, there seems to be no evidence on file to support this assertion.

In summary, the technical problem to be solved could only be regarded to reside in the provision of alternative oligonucleotides suitable for skipping of exon 53.

The solution consists of the oligonucleotides defined in claim 1.

The Opposition Division is of the opinion that the presently claimed subject matter would have been obvious in view of the teaching of D3 alone, since it discloses oligonucleotides targeting the same region and since it teaches the use of morpholino oligonucleotides with a length of up to 50 nucleotides in length (cf. D3, claims 1, 3, 10, 12). Merely extending the exemplified oligonucleotides by e. g. two nucleotides, as explicitly suggested in D3, does not require more than routine measures. In addition, the presently claimed compounds are not shown to possess any unexpected or surprising effects.

- 6.1.5 It is noted that the different auxiliary requests have different scopes (e. g. concerning the region(s) targeted), which may have a bearing on the inventive merit of the claimed subject matter. It is noted that D3 does not seem to suggest targeting the H53A (+23+47) region. However, this region is targeted in D4. While D4 refers to "*morpholine salts*" in paragraph 46, it is doubtful, whether this passage amounts to a direct disclosure of morpholinos.
- 6.1.6 In view of the replies of the parties to the summons to oral proceedings, the following further comments reflecting the *opinion* of the Opposition Division appear relevant.

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While the Proprietor has argued that the claimed subject matter was an improvement over the prior art, it was submitted in the letter dated 29 September 2017 (cf. page 6) "that the majority of the tested 20-mers ... show **at least equivalent or improved**, exon 53 skipping efficiency compared with h53AON1" (h53AON1 is an 18-mer; emphasis by the Proprietor). With some 20-mers merely being "equivalent", it appears that an improvement has not been shown to be present over the entire scope.

It is furthermore noted that all the tested oligonucleotides seem to be 100% complementary to their target, whereas the claims have a broader scope, namely encompassing oligonucleotides that are "specifically hybridisable" (cf. page 23 of the application as filed, last paragraph). In view of these considerations, the problem to be solved could only be regarded to reside in the provision of alternative oligonucleotides suitable for exon 53 skipping.

Article 106
Decisions subject to appeal

- (1) An appeal shall lie from decisions of the Receiving Section, Examining Divisions, Opposition Divisions and the Legal Division. It shall have suspensive effect.
- (2) A decision which does not terminate proceedings as regards one of the parties can only be appealed together with the final decision, unless the decision allows a separate appeal.
- (3) The right to file an appeal against decisions relating to the apportionment or fixing of costs in opposition proceedings may be restricted in the Implementing Regulations.

Rule 97
Appeal against apportionment and fixing of costs

- (1) The apportionment of costs of opposition proceedings cannot be the sole subject of an appeal.
- (2) A decision fixing the amount of costs of opposition proceedings cannot be appealed unless the amount exceeds that of the fee for appeal.

Rule 98
Surrender or lapse of the patent

The decision of an Opposition Division may be appealed even if the European patent has been surrendered in all the designated Contracting States or has lapsed in all those States.

Article 107
Persons entitled to appeal and to be parties to appeal proceedings

Any party to proceedings adversely affected by a decision may appeal. Any other parties to the proceedings shall be parties to the appeal proceedings as of right.

Article 108
Time limit and form

Notice of appeal shall be filed, in accordance with the Implementing Regulations, at the European Patent Office within **two months** of notification of the decision. Notice of appeal shall not be deemed to have been filed until the fee for appeal has been paid. Within **four months** of notification of the decision, a statement setting out the grounds of appeal shall be filed in accordance with the Implementing Regulations.

Further information concerning the filing of an appeal

- (a) Notice of appeal can be filed in accordance with Rule 1 and Rule 2(1) EPC, by delivery by hand, by post, or by technical means of communication. The filing has to comply with the details and conditions and, where appropriate, any special formal or technical requirements laid down by the President of the European Patent Office (R. 99(3) EPC).
- (b) The addresses of the filing offices of the European Patent Office are as follows:

(i) European Patent Office D-80298 Munich Germany Fax: +49 89 2399-4465	(ii) European Patent Office Postbus 5818 NL-2280 HV Rijswijk (ZH) The Netherlands Fax: +31 70 340-3016	(iii) European Patent Office D-10958 Berlin Germany Fax: +49 30 259 01-840
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- (c) The notice of appeal must contain the name and address of the appellant in accordance with the provisions of Rule 41(2)(c) EPC, an indication of the decision impugned, and a request defining the subject of the appeal. In the statement of grounds of appeal the appellant shall indicate the reasons for setting aside the decision impugned, or the extent to which it is to be amended, and the facts and evidence on which the appeal is based (R. 99(1) and (2) EPC). The notice of appeal and any subsequent submissions stating the grounds for appeal must be signed (R. 50(3) EPC).
- (d) The fee for appeal is laid down in the Rules relating to Fees. The schedule of fees and expenses of the EPO or a reference to the current version is regularly published in the Official Journal of the European Patent Office under the heading "Guidance for the payment of fees, expenses and prices". Fee information is also published on the EPO website under www.epo.org/fees.

Patentanmeldung Nr.
Patent application No.
Demande de brevet n°

10004274.6

Literaturbogen

Citation sheet

Liste des antériorités

- D1 Corey et al., Genome Biology, 2001, 2(5) 1015.1-1015.3
- D2 AU 2004903474 (priority document)
- D3 WO 2004/083432
- D4 WO 2004/048570 (\triangle EP 1 568 769)
- D5 CA 2 507 125
- D6 Aartsma-Rus et al., Human Molecular Genetics (2003), vol. 12, no. 8; pp 907-914
- D7 Aartsma-Rus et al., Neuromuscular Disorders vol.12,S71-S77(2002)
- D8 experimental report

D8-1 experimental report

- D9 - Popplewell *et al* (*Neuromuscular Disorders*, 2010, 20: 102-110)
- D10 - Aartsma-Rus *et al.*, *Oligonucleotides* 2005 Dec;15(4):284-97
- D11 - Figure A - showing the target region of exon 53 and the locations of the most active Popplewell (D9) PMOs compared to the exon 53 antisense oligonucleotides (AONs) SEQ ID NOs: 191, 192, 193 and 195 of the Opposed Patent
- D12 - Figures showing in two sets of experiments the efficacy of an AON targeting annealing site H53A (+39+62) (SEQ ID No: 192), an AON targeting annealing site H53A(+39+69) (SEQ ID No: 193) and an AON targeting annealing site H53A(+23+47) (SEQ ID No: 195) compared to an AON targeting the same exon 53 annealing site as h53AON1
- D13 - US 2013/0211062
- D14 - Declaration of Dr. Schnell
- D15 - Summerton and Weller, *Antisense & Nucleic Acid Drug Dev.* 1997, 7, 187-195.
- D16 experimental report (filed as D13 by the Opponent)



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Application No. / Patent No. 10 004 274.6 - 1401 / 2 206 781 /	Ref. X109014EPA AAW	Date 19.12.2017
Proprietor THE UNIVERSITY OF WESTERN AUSTRALIA		

Provision of a copy of the minutes in accordance with Rule 124(4) EPC

The attached copy of the minutes of the oral proceedings is sent to you in accordance with Rule 124(4) EPC.



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Enclosure(s): Copy of the minutes (Form 2309)



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Application No.:

10 004 274.6

Patent No.:

EP-B-2 206 781

Minutes of the oral proceedings before the OPPOSITION DIVISION

The proceedings were public.

Proceedings opened on 30.11.2017 **at** 09:33 **hours**

Present as members of the opposition division:

Chairman:	Macchia, Giovanni
1st member:	Bucka, Alexander
2nd member:	Romano, Alper
Minute writer:	Romano, Alper

Present as or for the party or parties:

- * For the Proprietor(s): THE UNIVERSITY OF WESTERN AUSTRALIA
 - a) Aylsa Williams (D. Young & Co) and Garreth Duncan (EPA), as professional representatives
 - b) Ch. Verni and M. Evans US patent attorneys for Sarepta Therapeutics (licensee), F. Schnell as technical expert
- * For the Opponent 1: Nippon Shinyaku Co., Ltd.
 - a) Günter Keller of Lederer & Keller (professional representative)
 - b) A. Naito (interpreter), T. Imazato as Patent Attorney (Abe, Ikubo & Katayama), A. Nakamura (patent attorney), N. Watanabe, Y. Shirouchi all f Nippon Shinyaku

The identity of the person/s (as well as, if applicable, that of the witness or witnesses) and, where necessary, the authorisation to represent/authority to act were checked.

Essentials of the oral proceedings and relevant statements of the parties:

Datum
Date 19.12.2017
DateBlatt
Sheet 1
FeuilleAnmelde-Nr:
Application No: 10 004 274.6
Demande n°:

The Chairman opened the proceedings and confirmed the requests on file. The opponent (OPP) requested the revocation of the patent under Art. 100(a) EPC in conjunction with Art. 56 EPC, Art. 100(b) EPC and Art. 100(c) EPC. The proprietor (PRO) requested rejection of the opposition, i.e. maintenance of the patent as granted based on the main request (MR) or alternatively maintenance of the patent on the basis of auxiliary requests 1-5 (AR1-5). The Chairman also noted that D1-D8 was submitted by the OPP with the notice of opposition, D9-D12 was filed by the PRO with reply to the notice and D13-D15 was filed in reply to the summons. D13 filed by the opponent was renumbered as D16.

The first objection to be discussed was added matter under Art. 100(c) EPC. OPP noted that they relied on their arguments indicated in writing. Claim 1 of the MR had four different issues:

- 1- The morpholino modification of claim 1 was not properly disclosed in the application. The only basis for morpholino was the legend of table 1a, on bridging passage of pages 16-17. Additionally the general passage on page 26 starting from line 15 disclosed PNA modifications but did not mention morpholino. Finally the table 39 on page 62 also did not disclose morpholinos.
- 2- The term 'both' was not disclosed anywhere in the application. The term 'weasel' was disclosed but this term was related to skipping of more than one exon. Table 1c on pages 17-18 disclosed weasels always as 2 oligonucleotides linked by poly(A). In any case there was no weasel disclosed for the claimed target regions.
- 3- The nucleotide range of 20-31 was disclosed only on page 21, lines 12-15 in the context of another exon (exon 19) and not exon 53.
- 4- The term 'specifically hybridizable' as defined on page 23, starting from line 18 could not have been combined with the disclosure of table 39.

PRO replied to the OPP that the term morpholino was disclosed on page 17 but was not linked to table 1a; it was a general disclosure. Everyone in the field knew what morpholino chemistry meant, D15 was filed as evidence for that knowledge (D15: page 188, figure 2). PRO also cited case law decisions T714/00 and T1067/97 as support for allowing combination of features. In this case the base sequence and the backbone chemistry were not inextricably linked. The passage on page 26, line 30 states 'one such modification' and therefore PNA was disclosed there only as an example.

Datum
Date 19.12.2017
DateBlatt
Sheet 2
FeuilleAnmelde-Nr:
Application No: 10 004 274.6
Demande n°:

PRO was also of the opinion that the term 'both' was disclosed because the case law such as T667/08 did not require literal support and forming a range from the target positions was permitted as indicated in T201/83. The sequences on page 62 formed a cluster. The position +23 was purely a starting point, +69 was the end point of the annealing site. These positions were used to define the coordinate points.

According to PRO the nucleotide range of 20-31 was also not linked to exon 19 but was a general feature. That passage on page 21, line 13 used the wording 'such as' indicating exon 19 as an example. Likewise 'specifically hybridizable' was also a general term clearly disclosed on page 23.

OPP responded that although the skilled person might have known that 2'-OMe could be replaced with morpholino, however under Art. 100(c) EPC the issue was whether there was a direct and unambiguous basis in the application as originally filed. OPP also objected the citation of several case law decisions because it was difficult extract information from the case law book. This should be allowed only in exceptional cases. Moreover, table 39 on page 62 disclosed many regions and there was no clear disclosure of the ranges of claim 1. Finally, the objection about the term 'specifically hybridizable' was also maintained.

PRO replied that the skilled person would have taken the common general knowledge into account. Any antisense oligonucleotide could be morpholino. The cited case law decisions were well known cases. In table 39 4/7 had exon skipping activity at 50nM. Therefore the combination was justified.

After a break between 10:45-11:15, the chairman declared that requirements of Art. 100(c) EPC were not met. At the request of further explanation by the PRO, the Opposition Division indicated that the range 20-31 nucleotides and the term 'both' did not have a basis and, in the context of claim 1 the term morpholino also had no basis. It was further noted that this conclusion also applied to AR1-5.

The PRO asked for a short break and between 11:18-11:23 a break was given.

After the break, the PRO declared that he/she chose not to file any further requests and no requests on file were withdrawn.

The chairman declared the revocation of the patent for non-fulfilment of the requirements of Art. 100(c) EPC and closed the proceedings.

Sheet 2/1

Application No.: 10 004 274.6

After deliberation of the opposition division,

• the chairman announced the following **decision**:

"The European patent is revoked."

Regarding the reasons for the decision, the chairman referred to:

Article 101(2) EPC, first sentence: the following ground(s) for opposition mentioned in Article 100 EPC prejudice(s) the maintenance of the patent as granted.

The division's opinion is that, even taking into consideration the amendments made by the proprietor of the patent during the opposition proceedings, the patent does **not** meet the requirements of the Convention (Article 101(3)(b)EPC)

The party/parties was/were informed that the minutes of the oral proceedings and a written reasoned decision (including an indication of the possibility of appeal) will be notified to him/them as soon as possible.

The chairman **closed the oral proceedings** on 30.11.2017 at 11:25 hours.

signed:

Macchia, Giovanni

.....
Chairman

Enclosure(s):



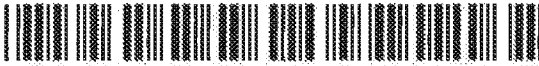
signed:

Romano, Alper

.....
Minute Writer



Questions about this communication ?

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D Young & Co LLP
120 Holborn
London EC1N 2DY
ROYAUME UNI

Date

19.12.2017

Reference X109014EPA AAW	Application No./Patent No. 10004274.6 - 1401 / 2206781
Applicant/Proprietor THE UNIVERSITY OF WESTERN AUSTRALIA	

EPA/EPO/OEB Formblatt/Form/Formulaire : 2331

Empfangsbescheinigung über den Zugang des vorstehend bezeichneten Schriftstücks
Acknowledgement of receipt of the document specified above
Récépissé du document spécifié ci-dessus

Unter Bezugnahme auf die Mitteilung im ABI EPA 7/2010, 377 wird gebeten, die Empfangsbescheinigung mit Empfangsdatum und Unterschrift zu versehen und **umgehend** an das EPA zurückzusenden:

With reference to the Notice in OJ EPO 7/2010, 377, you are requested to date and sign the acknowledgement of receipt and return it to the EPO **immediately**:

Conformément au communiqué paru au JO OEB 7/2010, 377, vous êtes prié d'indiquer sur le récépissé la date de réception du document, de signer le récépissé et de le renvoyer **sans délai** à l' OEB:

- **über die Online-Dienste des EPA** (als Anlage zu EPA Form 1038) / **through EPO Online Services** (as annex to EPO Form 1038) / **par les services en ligne de l'OEB** (en tant que pièce jointe au formulaire OEB 1038),
- **per Fax / by fax / par téléfax** (+49 (0) 89 2399-4465 or +31 (0) 70 340-3016)
- **oder per Post / or by post / ou par courrier.**

Empfangen am / Received on / Reçu le :

Unterschrift / Signature:

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le destinataire ou la personne dûment mandatéeRücksende-Adresse / Return address / Adresse de retour
(Umschlag / envelope / enveloppe ISO C4 / DL / C6/C5 / C6)DEUTSCHLAND
80298 MUNICH
Europäisches Patentamt

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European Patent Office
80298 MUNICH
GERMANY

Questions about this communication ?

Contact Customer Services at www.epo.org/contact



D Young & Co LLP
120 Holborn
London EC1N 2DY
ROYAUME UNI

DEADLINE: No Due Date

REVIEW:

ACTION: Extended Search Report

ATTORNEY: AAW

Added by Francesca Iacob @ 4:28 pm, Jan 30, 2017

Date

23.01.17

Reference P110313EPAA	Application No./Patent No. 16172354.9 - 1401
Applicant/Proprietor Sarepta Therapeutics, Inc.	

Communication

The extended European search report is enclosed.

The extended European search report includes, pursuant to Rule 62 EPC, the European search report (R. 61 EPC) or the partial European search report/ declaration of no search (R. 63 EPC) and the European search opinion.

Copies of documents cited in the European search report are attached.

☒ 0 additional set(s) of copies of such documents is (are) enclosed as well.

The following have been approved:

☒ Abstract ☒ Title

☐ The Abstract was modified and the definitive text is attached to this communication.

The following figure(s) will be published together with the abstract:

Refund of search fee

If applicable under Article 9 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.

Should you wish to further prosecute this application in the examination phase, your attention is drawn to the provisions of Rule 70a EPC. An invitation to respond to the extended European search report will be issued once the date of publication of the European search report has been mentioned in the European Patent Bulletin (R. 69(1), R. 70(2) EPC).





EUROPEAN SEARCH REPORT

Application Number
EP 16 17 2354

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	WO 2006/000057 A1 (UNIV WESTERN AUSTRALIA [AU]; WILTON STEPHEN DONALD [AU]; FLETCHER SUE) 5 January 2006 (2006-01-05) * page 62; figure 22; tables 37,38 * -----	1-12	INV. C12N15/113 C12N15/11
			TECHNICAL FIELDS SEARCHED (IPC)
			C12N
The present search report has been drawn up for all claims			
Place of search The Hague		Date of completion of the search 12 January 2017	Examiner Romano, Alper
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

1
EPO FORM 1503 03.82 (P04C01)

SRPT-VYDS-0004840

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 16 17 2354

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

12-01-2017

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
W0 2006000057 A1	05-01-2006	AT 498685 T	15-03-2011
		CY 1111447 T1	05-08-2015
		DK 1766010 T3	06-06-2011
		DK 2206781 T3	07-03-2016
		EP 1766010 A1	28-03-2007
		EP 2206781 A2	14-07-2010
		EP 2500430 A2	19-09-2012
		EP 2933332 A1	21-10-2015
		EP 3029142 A1	08-06-2016
		ES 2361325 T3	16-06-2011
		ES 2564185 T3	18-03-2016
		HK 1216545 A1	18-11-2016
		HR P20110352 T1	30-06-2011
		HR P20160225 T1	06-05-2016
		PT 1766010 E	25-05-2011
		SI 1766010 T1	30-06-2011
		SI 2206781 T1	31-05-2016
		US 2008200409 A1	21-08-2008
		US 2011015253 A1	20-01-2011
		US 2011015258 A1	20-01-2011
		US 2011046203 A1	24-02-2011
		US 2011263686 A1	27-10-2011
		US 2012022144 A1	26-01-2012
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		US 2012029057 A1	02-02-2012
		US 2012029058 A1	02-02-2012
		US 2012029059 A1	02-02-2012
		US 2012029060 A1	02-02-2012
		US 2012041050 A1	16-02-2012
		US 2013116310 A1	09-05-2013
		US 2013217755 A1	22-08-2013
		US 2013253033 A1	26-09-2013
		US 2013253180 A1	26-09-2013
		US 2013274313 A1	17-10-2013
		US 2013331438 A1	12-12-2013
		US 2014080898 A1	20-03-2014
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		US 2014243516 A1	28-08-2014
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		US 2014309284 A1	16-10-2014
		US 2014309285 A1	16-10-2014
		US 2015057330 A1	26-02-2015
		US 2015353931 A1	10-12-2015
		US 2015376615 A1	31-12-2015
		US 2015376616 A1	31-12-2015

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 16 17 2354

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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12-01-2017

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		US 2016002631 A1	07-01-2016
		US 2016002632 A1	07-01-2016
		US 2016002635 A1	07-01-2016
		W0 2006000057 A1	05-01-2006

Information on Search Strategy - Pilot phase (see OJ 2015, A86)

The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number

EP 16 17 2354

TITLE: MULTIPLE EXON SKIPPING COMPOSITIONS FOR DMD

APPLICANT: Sarepta Therapeutics, Inc.

IPC CLASSIFICATION: C12N15/113, C12N15/11

EXAMINER: Romano, Alper

CONSULTED DATABASES: DOSYS, EPODOC, INET (GOOGLE), MEDLINE, NPL, WPI, XFULL

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC:

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:

claims directed to morpholino antisense oligonucleotide targeting exon 52 of dystrophin to induce exon 52 skipping. All SEQ ID NOS of claim 1 searched.

Datum		Blatt		Anmelde-Nr:	
Date	cf Form 1507	Sheet	1	Application	16 172 354.9
Date		Feuille		No:	
				Demande n°:	

The search opinion is being carried out on the **following application documents**

Description, Pages

1-114 as originally filed

Sequence listings, SEQ ID NO

1-651 as originally filed

Claims, Numbers

1-12 as originally filed

Drawings, Sheets

1-39 as originally filed

Reference is made to the following document; the numbering will be adhered to in the rest of the procedure.

D1 WO 2006/000057 A1 (UNIV WESTERN AUSTRALIA [AU]; WILTON
STEPHEN DONALD [AU]; FLETCHER SUE) 5 January 2006

The divisional application meet the requirement of Art. 76(1) EPC.

The search report and the search opinion are established with the assumption that the priority rights are valid (Art. 89 EPC).

Present claims 1-12 are novel, the prior art does not disclose any antisense oligonucleotides (AONs) targeting exon 52 of the dystrophin gene for exon skipping and any such AONs containing morpholino subunits (Art. 54 EPC).

Datum
Date cf Form 1507
Date

Blatt
Sheet 2
Feuille

Anmelde-Nr:
Application 16 172 354.9
No:
Demande n°:

D1 can be considered as the closest prior art. D1 discloses 2-OMe modified antisense oligonucleotides (AONs) successfully targeting exon 52 of the dystrophin gene for exon skipping (D1: table 1A, 37,38, figure 22). The subject matter of claim 1 differs from that of D1 in that AONs containing morpholino subunits are suggested for the same purposes. There is no technical effect disclosed due to this difference.

In view of D1 the problem underlying present claims can be defined as the provision of alternative modified AONs for skipping exon 52.

The solution is AONs containing morpholino subunits and comprising base sequences of SEQ ID NOS:372-415

The application does not provide any technical evidence that the claimed compounds have any exon skipping activity. The subject matter of present claims is rather obvious because morpholino modifications are well known in the exon skipping field as one of the most common alternatives for 2'-OMe modification. In fact, D1 also suggest that morpholino could be used instead of 2-OMe (D1: legend of table 1A, page 17). The presence of sequence IDs in claim 1 also do not provide any additional contribution because the regions of dystrophin gene that could be targeted for exon skipping are well established. The remaining claims are directed to routine modifications or uses in the field. In the absence of any unexpected effect or improvement over the prior art, claims 1-12 do not involve an inventive step (Art. 56 EPC).

Claims 1-12 are industrially applicable (Art. 57 EPC).



Questions about this communication ?

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D Young & Co LLP
120 Holborn
London EC1N 2DY
ROYAUME UNI

DEADLINE: No due date

REVIEW:

ACTION: Extended Search Report

ATTORNEY: AAW

Added by Jessica Cook @ 12:00 pm, Aug 31, 2017

Date

05.09.17

Reference P109014EPAAA	Application No./Patent No. 17159328.8 - 1401
Applicant/Proprietor THE UNIVERSITY OF WESTERN AUSTRALIA	

Communication

The extended European search report is enclosed.

The extended European search report includes, pursuant to Rule 62 EPC, the European search report (R. 61 EPC) or the partial European search report/ declaration of no search (R. 63 EPC) and the European search opinion.

Copies of documents cited in the European search report are attached.

☒ 0 additional set(s) of copies of such documents is (are) enclosed as well.

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☒ Abstract ☒ Title

☐ The Abstract was modified and the definitive text is attached to this communication.

The following figure(s) will be published together with the abstract:

Refund of search fee

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EUROPEAN SEARCH REPORT

Application Number
EP 17 15 9328

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	CA 2 507 125 A1 (MATSUO MASAFUMI [JP]; TAKESHIMA YASUHIRO [JP]; NONPROFIT ORGANIZATION) 10 June 2004 (2004-06-10) * sequences 69,70,75 * * examples 81,87 *	1-5	INV. C12N15/113 A61K31/7088 A61K31/712
A	AARTSMA-RUS, A. ET AL.: "Therapeutic antisense-induced exon skipping in cultured muscle cells from six different DMD patients", HUMAN MOLECULAR GENETICS, vol. 12, no. 8, 2003, pages 907-914, XP008084159, ISSN: 0964-6906 * compound h53A0N1 *	1-5	ADD. C07H21/00 A61K48/00
A	AARTSMA-RUS A ET AL: "Targeted exon skipping as a potential gene correction therapy for Duchenne muscular dystrophy", NEUROMUSCULAR DISORDERS,, vol. 12, 2002, pages 71-77, XP008116183, DOI: 10.1016/S0960-8966(02)00086-X * compound h53A0N1 *	1-5	TECHNICAL FIELDS SEARCHED (IPC) C12N A61K
A	MATSUO M: "DUCHENNE AND BECKER MUSCULAR DYSTROPHY: FROM GENE DIAGNOSIS TO MOLECULAR THERAPY", IUBMB LIFE, vol. 53, no. 3, 1 March 2002 (2002-03-01), pages 147-152, XP009021242, ISSN: 1521-6543 * the whole document *	1-5	
X,P	WO 2004/083446 A2 (ACADEMISCH ZIEKENHUIS LEIDEN [NL]; VAN OMMEREN GARRIT-JAN BOUDEWI [NL]) 30 September 2004 (2004-09-30) * the whole document *	1-5	
The present search report has been drawn up for all claims			
Place of search The Hague		Date of completion of the search 28 August 2017	Examiner Andres, Serge
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

1
EPO FORM 1503 03.82 (P04C01)

SRPT-VYDS-0004847

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 17 15 9328

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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28-08-2017

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
CA 2507125	A1	10-06-2004	AU 2003284638 A1	18-06-2004
			CA 2507125 A1	10-06-2004
			CA 2796924 A1	10-06-2004
			CA 2942791 A1	10-06-2004
			EP 1568769 A1	31-08-2005
			EP 2135948 A2	23-12-2009
			EP 2374885 A2	12-10-2011
			EP 2386636 A2	16-11-2011
			EP 2392660 A2	07-12-2011
			EP 2530153 A1	05-12-2012
			EP 2530154 A1	05-12-2012
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			EP 2530156 A1	05-12-2012
			ES 2509140 T3	17-10-2014
			ES 2554660 T3	22-12-2015
			ES 2561851 T3	01-03-2016
			ES 2566628 T3	14-04-2016
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			JP 2010229132 A	14-10-2010
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			JP 2016182122 A	20-10-2016
			JP W02004048570 A1	23-03-2006
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			US 2011046360 A1	24-02-2011
			US 2013090465 A1	11-04-2013
			US 2014316123 A1	23-10-2014
			US 2016002636 A1	07-01-2016
			W0 2004048570 A1	10-06-2004

W0 2004083446	A2	30-09-2004	AU 2003225410 A1	11-10-2004
			AU 2004221495 A1	30-09-2004
			AU 2009240879 A1	17-12-2009
			CA 2519863 A1	30-09-2004
			CA 2524255 A1	30-09-2004
			CA 2855229 A1	30-09-2004
			EP 1606407 A2	21-12-2005
			ES 2452293 T3	31-03-2014
			HK 1084694 A1	04-04-2014
			JP 5378423 B2	25-12-2013

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 17 15 9328

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

28-08-2017

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		JP 5973477 B2	23-08-2016
		JP 2006523101 A	12-10-2006
		JP 2011101655 A	26-05-2011
		JP 2014138589 A	31-07-2014
		NZ 543115 A	31-01-2008
		US 2006099616 A1	11-05-2006
		US 2006147952 A1	06-07-2006
		US 2009076246 A1	19-03-2009
		US 2011312086 A1	22-12-2011
		US 2013072671 A1	21-03-2013
		US 2013302806 A1	14-11-2013
		US 2014213635 A1	31-07-2014
		US 2014275212 A1	18-09-2014
		US 2014357698 A1	04-12-2014
		US 2014357855 A1	04-12-2014
		US 2014378527 A1	25-12-2014
		US 2015218559 A1	06-08-2015
		US 2016168570 A1	16-06-2016
		US 2016194636 A1	07-07-2016
		US 2016251658 A1	01-09-2016
		US 2016355810 A1	08-12-2016
		WO 2004083432 A1	30-09-2004
		WO 2004083446 A2	30-09-2004

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

Information on Search Strategy - Pilot phase (see OJ 2015, A86)

The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number

EP 17 15 9328

TITLE: ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

APPLICANT: THE UNIVERSITY OF WESTERN AUSTRALIA

IPC CLASSIFICATION: C12N15/113, A61K31/7088, A61K31/712, C07H21/00, A61K48/00

EXAMINER: Andres, Serge

CONSULTED DATABASES: BIOSIS, DOSYS, EMBASE, EPODOC, MEDLINE, NPL, WPI, XPRD

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC:

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:

Antisense oligonucleotides targeting regions H53A(+23+47) and/or H53A(+39+69) of exon 53 for inducing exon skipping in the dystrophin gene in order to treat Duchenne's muscular dystrophy (DMD).

Datum
Date cf Form 1507
Date

Blatt
Sheet 1
Feuille

Anmelde-Nr:
Application 17 159 328.8
No:
Demande n°:

The examination is being carried out on the **following application documents**

Description, Pages

1-67 as originally filed

Sequence listings, SEQ ID NO

1-212 as originally filed

Claims, Numbers

1-5 filed in electronic form on 31-05-2017

Drawings, Sheets

1/22-22/22 as originally filed

Reference is made to the following documents; the numbering will be adhered to in the rest of the procedure.

- D1 CA 2 507 125 A1 (10 June 2004)
 - D2 HUMAN MOLECULAR GENETICS, vol. 12, (2003), pages 907-914 [XP008084159]
 - D3 NEUROMUSCULAR DISORDERS, vol. 12, (2002), pages 71-77 [XP008116183]
 - D4 IUBMB LIFE, vol. 53, (March 2002), pages 147-152 [XP009021242]
 - D5 WO 2004/083446 A2 (30 September 2004)
-

Datum
Date cf Form 1507
Date

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Sheet 2
Feuille

Anmelde-Nr:
Application 17 159 328.8
No:
Demande n°:

1 **DIVISIONAL** (Art. 76 EPC)

The subject-matter of present application does not extend beyond the content of the earlier application as filed and fulfils therefore the requirements of Art. 76(1) EPC.

2 **AMENDMENTS** (Art.123 EPC)

The amendments filed with the letter dated 31.05.2017 do comply with the requirements of Article 123(2) EPC.

3 **PRIORITY** (Art. 87-89 EPC), **NOVELTY** (Art. 54 EPC)

3.1 The subject-matter now claimed has not been found back in AU2004903474 which serves as a basis for claiming priority rights. The date for assessment of the patentability of the presently claimed subject-matter is therefore the filing date of the parent application, i.e. 28.06.2005. As a consequence, document D5 (published on 30.09.2004) forms part of the prior art according to Art. 54(2) EPC.

3.2 None of the available prior art documents does disclose an exon-skipping antisense oligonucleotide targeting exon 53 of the human dystrophin pre-mRNA in the region defined by nucleotides 23 to 69 and having a length between 20 and 31 nucleotides. Hence, the subject-matter of present claims 1-5 is considered as novel in the sense of Art. 54 EPC.

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Anmelde-Nr:
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No:
Demande n°:

4 **INVENTIVE STEP** (Art. 56 EPC)

- 4.1 Document D5 is considered as being the closest prior art to the subject-matter of present independent claims 1, 3 and 4. This document discloses h53AON1, which targets nucleotides 45-62 of exon 53 of the human dystrophin pre-mRNA, and its use in skipping of said exon for the treatment of DMD.
- 4.2 The subject-matter of claims 1,3 and 4 therefore differs from this known teaching in that the exon-skipping oligonucleotides have a length between 20 and 31 nucleotides. The problem to be solved by the present invention may therefore be regarded as alternative (improved ?) exon-skipping antisense oligonucleotides targeting exon 53 of the human dystrophin pre-mRNA in the region defined by nucleotides 23 to 69.
- 4.3 It is to be noted that the prior art discloses efficient exon-skipping antisense oligonucleotides targeting said specific region of exon 53 (see e.g. D1-D3,D5). In addition, D5 suggests several times that in order to enhance the efficiency of the oligonucleotides an increase in hybridisation length should be sought (see e.g. page 3, lines 18-29; page 10, lines 4-8; claim 3). Therefore, D5 puts the skilled person into a position where lengthening h53AON1, or the other oligonucleotides targeting the same region and disclosed in D1-D3, is an obvious step to produce exon-skipping oligonucleotides having higher efficiency with a reasonable expectation of success. Furthermore, are claimed SEQ IDs 192 and 193 fully covered by the juxtaposition of sequences 69 and 70 of D1, and does the addition of sequence 75 of D1 allow to have a quasi-complete coverage of the claimed region. Finally, the fact that the same region of exon 53 has been targeted by various oligonucleotides in several documents of the prior art, indicates as well that said region was considered to be a valuable target region when trying to obtain exon-skipping. Hence, the subject-matter of present claims 1,3 and 4 has to be seen as being merely obvious design variants of the oligonucleotides already disclosed in the prior art. Hence, the solution proposed in said claims (as well as in claims 2 and 5 depending thereon) cannot be considered to involve an inventive step (Articles 52(1) and 56 EPC).

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Date cf Form 1507
Date

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Sheet 4
Feuille

Anmelde-Nr:
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- 4.4 In addition, in view of pages 62 and 63, where skipping of exon 53 is disclosed, only SEQ ID 193 is shown to have a strong exon skipping effect. SEQ ID 192, which targets the same sequence but is shorter than SEQ ID 193, and SEQ ID 195 have only a very weak effect. Therefore, it is considered not to be credible that any antisense targeting said region of exon 53 would in fact solve the stated problem.

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Filed on behalf of: Junior Party **UNIVERSITY
OF WESTERN AUSTRALIA**

Paper No. _____

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Date filed: November 18, 2014

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UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT TRIAL AND APPEAL BOARD

University of Western Australia,
Junior Party
(Patent 8,455,636,
Inventors: Stephen Donald Wilton, Sue Fletcher and Graham McClorey)

v.

Academisch Ziekenhuis Leiden,
Senior Party
(Application 11/233,495,
Inventors: Garrit-Jan Boudewijn van Ommen, Judith Christina
Theodora van Deutekom, Johannes Theodorus den Dunnen and
Annemieke Aartsma-Rus).

Patent Interference No. 106,007 (RES)
(Technology Center 1600)

**UNIVERSITY OF WESTERN AUSTRALIA
NOTICE OF FILING PRIORITY STATEMENT**

1 MAIL STOP INTERFERENCE
2 United States Patent and Trademark Office
3 Patent Trial and Appeal Board
4 Madison Building East
5 600 Dulany Street
6 Alexandria, Virginia 22313

7 Your Honor:

8 Pursuant to 37 C.F.R. § 41.204 and the Order – Motion Times – 37 C.F.R. § 41.104(c),
9 dated July 18, 2014 (Paper 3), Junior Party University of Western Australia (“UWA”) hereby
10 notifies Senior Party Academisch Ziekenhuis Leiden that on this date, UWA filed a Priority
11 Statement.

12 Respectfully submitted,

13 Date: November 18, 2014

By: /s/ R. Danny Huntington
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/776,533	09/14/2015	Richard K. BESTWICK	AVN-017CPUS	2035
123147	7590	11/16/2017	EXAMINER	
Nelson Mullins Riley & Scarborough LLP/Sarepta One Post Office Square Boston, MA 02109			SHIN, DANA H	
			ART UNIT	PAPER NUMBER
			1674	
			NOTIFICATION DATE	DELIVERY MODE
			11/16/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

Application No.

14/776,533

Applicant(s)

BESTWICK et al.

Office Action Summary

Examiner

DANA H SHIN

Art Unit

1674

AIA Status

No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 28 August 2017

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____

2a) ☒ This action is **FINAL**.

2b) ☐ This action is non-final.

3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☒ Claim(s) 16-17 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☒ Claim(s) 16-17 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10) ☐ The specification is objected to by the Examiner.

11) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some** c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

3) ☐ Interview Summary (PTO-413)

Paper No(s)/Mail Date _____

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)

4) ☐ Other: _____

Paper No(s)/Mail Date _____

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DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on August 28, 2017.

Currently, claims 16-17 are pending and under examination on the merits in the instant application.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Information Disclosure Statement

Applicant's representative commented over the phone that one IDS was not considered by the examiner. The examiner was unable to identify an unconsidered IDS. Applicant is advised to specifically address/communicate the unconsidered IDS in writing by providing the image of the first page of the unconsidered IDS. Upon verification that the IDS was indeed not considered, the examiner will consider the IDS and mail the considered IDS.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

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Maintained Rejections

Claim Rejections - 35 USC § 102

Claims 16-17 remain rejected under 35 U.S.C. 102(e) as being anticipated by Watanabe et al. for the reasons of record as set forth in the Office action mailed on February 28, 2017 and for the reasons set forth below.

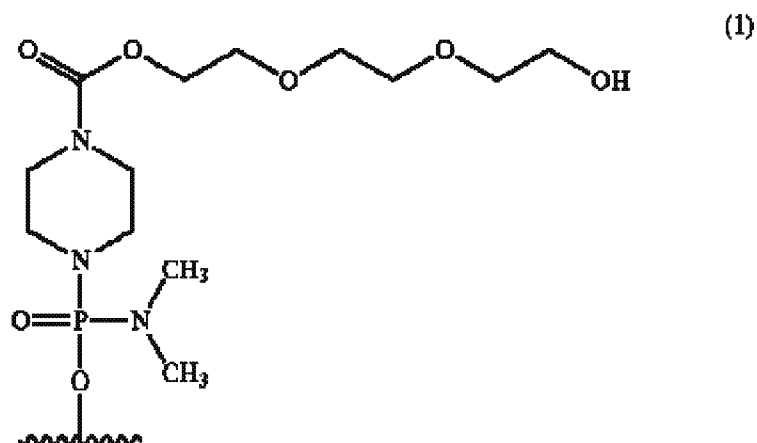
Applicant's arguments filed on August 28, 2017 have been fully considered but they are not persuasive. Applicant argues that Watanabe does not “explicitly” disclose the structure claimed in the instant case. Applicant then compares Watanabe’s 2’-O-methyl AON structure to the claimed PMO structure to show structural differences. In response, it is noted that the instant rejection is not based on Watanabe’s 2’-O-methyl structure. Now, note that the anticipation does not require actual performance or actual compound to be “explicitly” disclosed. The fact remains that Watanabe “explicitly” disclosed the instantly claimed PMO structure (see formula (I)) as well as the 5’ PEG conjugate structure (see Group (1)). It is true that the instantly claimed nucleotide sequence is expressly exemplified only as a 2’-O-methyl RNA oligonucleotide by Watanabe. However, the Watanabe publication expressly taught that exon-skipping oligonucleotide can be a 2’-O-methyl RNA oligonucleotide or PMO DNA oligonucleotide. As such, one of ordinary skill in the relevant art fully reading and understanding the teachings of the Watanabe reference would at once envisage and readily draw a 5’-PEG conjugated PMO structure having the claimed DNA sequence.

“If one of ordinary skill in the art is able to “at once envisage” the specific compound within the generic chemical formula, the compound is anticipated. One of ordinary skill in the art **must be able to draw** the structural formula or write the name of each of the compounds included in the generic formula before any of the compounds can be “at once envisaged.”” (emphasis added). See MPEP §2131.02.

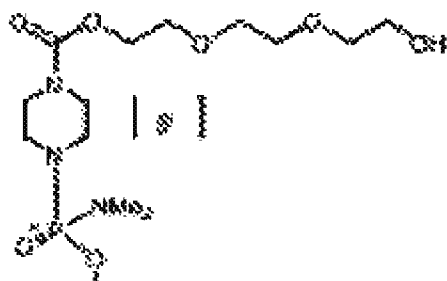
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Applicant argues that Watanabe's 5' PEG is "being fixed as hydroxyl" thus does not teach that the 5' end is "variable." The examiner fails to understand applicant's argument. The 5' end of the PMO antisense oligomer having formula (I) is disclosed as following in paragraph 0162 of Watanabe:



Now, compare the above structure to the instantly claimed 5' end as directly copied from the fuzzy structure as submitted in the claims by applicant:



As far as the examiner can see, there is no structural difference between the two 5' terminal PEG moieties conjugated to the 5' end of the PMO unit, unless the examiner is missing a structural element in the fuzzy structure in the claims.

Applicant then goes over Watanabe's paragraphs 0021 and 0082 to attack that Watanabe disclosed various target regions/lengths and "a long laundry list of possible nucleobases". The examiner fails to understand the relevance of applicant's arguments. The instant anticipation rejection is based on the explicitly disclosed exon 53 skipping nucleotide sequence, which is SEQ ID NO:57 thus the mere fact that Watanabe disclosed other target regions/lengths and

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nucleobases does not show that the claimed nucleotide sequence having PMO units and a 5' terminal PEG conjugate is not taught by Watanabe's reference.

In view of the foregoing, this rejection is maintained.

Claim Rejections - 35 USC § 103

Claims 16-17 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Watanabe et al. for the reasons of record as set forth in the Office action mailed on February 28, 2017 and for the reasons set forth below.

Applicant's arguments filed on August 28, 2017 have been fully considered but they are not persuasive. Applicant argues that the examiner failed to provide a reason as to why one of ordinary skill in the art would have selected Watanabe's H53_36-60 as a "lead compound" with a reasonable expectation of success. In particular, Applicant points out the Otsuka case (Fed. Cir. 2012) and argues that a compound cannot be a lead compound when other compounds having "higher activity" are available. In response, it is noted that there is no *per se* rule that requires a selection of a single lead compound for obviousness under §103. See MPEP §2143: The Federal Circuit in *Eisai* makes it clear that from the perspective of the law of obviousness, **any known compound might possibly serve as a lead compound...**It should be noted that the **lead compound cases do not stand for the proposition that identification of a single lead compound is necessary in every obviousness rejection of a chemical compound.**" (emphasis added). Further, applicant did not point out how the Otsuka case (Fed. Cir. 2012) is relevant and analogous to the instant rejection. Note that in *Otsuka*, the claims at issue pertain to an antipsychotic compound and the Courts have determined that one of ordinary skill in the art would not have selected the prior art "OPC-4392" compound for modification because the prior art compound "did **not** treat positive symptoms of schizophrenia" thus the prior art compound "was viewed as **lacking "antipsychotic component"**", and furthermore, the prior art compound

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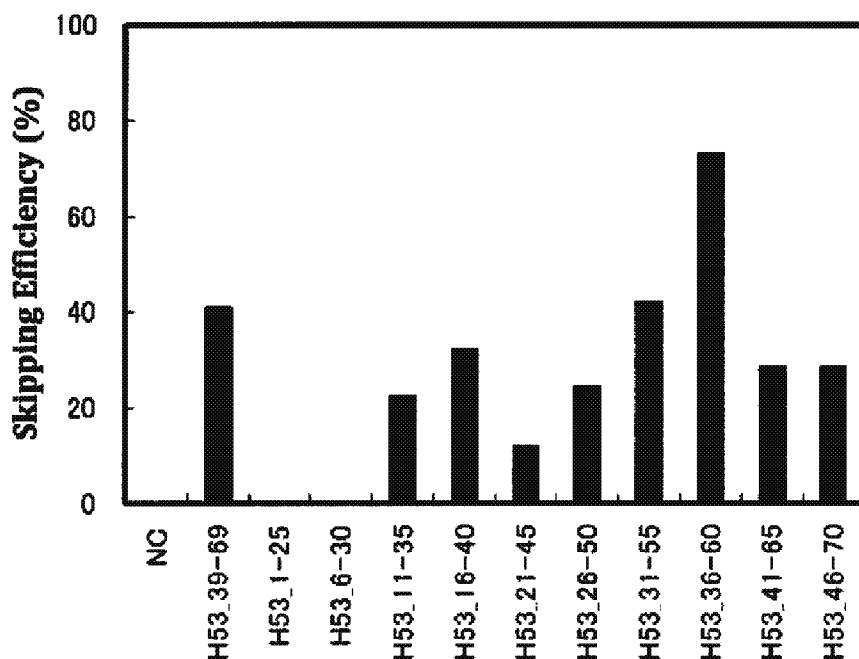
“was likely to **cause patients to act out their delusions and hallucinations**”, thereby aggravating psychotic symptoms hence has pro-psychotic, not anti-psychotic, activity. Hence, both the district court and the Federal Circuit found that “the prior art **taught away** from using OPC-4392 as a starting point for further antipsychotic research.” (emphasis added). In the instant case, there is no teaching in Watanabe that SEQ ID NO:57 cannot have a PMO modification or that SEQ ID NO:57 lacks exon 53 skipping activity. That is, Watanabe does not provide any disclosure that teaches away from using the 25-mer sequence as an exon 53 skipping oligonucleotide modified with PMO and a 5'-PEG conjugate. As such, there is no analogy/similarity between the fact pattern of the instant case and that of the Otsuka case. As such, the examiner finds applicant’s heavy reliance on the Otsuka case irrelevant and unpersuasive.

In fact, in stark contrast to the “OPC-4392” prior art compound that was deemed unsuitable as a compound to be selected for further modification in *Otsuka* since it displayed pro-psychotic properties instead of anti-psychotic properties, Watanabe’s SEQ ID NO:57 (“H53_36-60”) showed one of the greatest exon 53 skipping efficiency at about 80%-90% compared to other oligonucleotides. Hence, Watanabe’s SEQ ID NO:57 was one of oligonucleotides having “higher activity” therefore applicant’s argument that a compound cannot be a lead compound when other compounds having “higher activity” are available is not found persuasive. See Watanabe’s Figure 9 as copied below:

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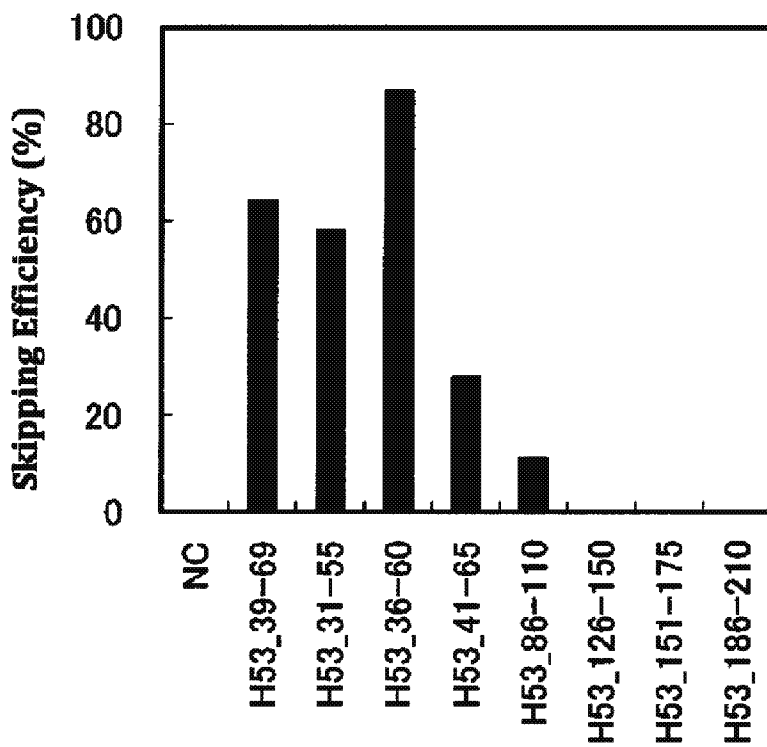
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Figure 9



See also Figure 13 demonstrating that SEQ ID NO:57 showed the highest level of exon 53 skipping efficiency:

Figure 13



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In view of the foregoing, the examiner finds applicant's arguments made in comparison to the Otsuka case completely unpersuasive and the examiner fails to understand why the non-analogous Otsuka case that is repeatedly mentioned and addressed throughout the remarks should be even considered in the instant case. It is noted that all of applicant's arguments pertaining to the Otsuka case bear no merit whatsoever for the reasons stated hereinabove.

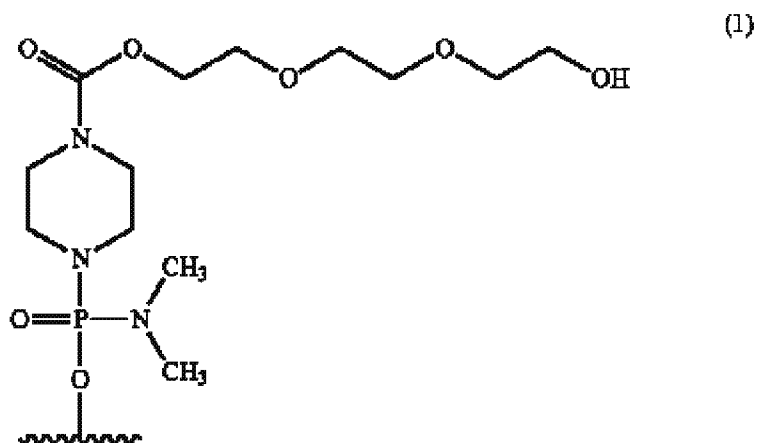
Further, in view of the expressly demonstrated efficient exon 53 skipping activity pertaining to Watanabe's SEQ ID NO:57 ("H53_36-60"), applicant's arguments addressing "unpredictable" AON activity thus lack of reasonable expectation of success by further pointing out various documents at pages 16-18 of the remarks are found unpersuasive and irrelevant. Note that the documents pointed out by applicant cannot rebut or nullify the results obtained by Watanabe's SEQ ID NO:57 ("H53_36-60") as illustrated in the above Figures thus there is no objective, factual evidence that supports applicant's alleged high level of unpredictability and lack of reasonable expectation of success pertaining to an oligonucleotide targeted to "H53_36-60".

Applicant argues that there is no reason/motivation to select Watanabe's SEQ ID NO:57 as a lead compound. Again, there is no legal requirement that a selection of a "lead compound" is necessary for §103. The fact remains that Watanabe's antisense oligonucleotide targeted to human dystrophin exon 53 at positions 36-60 (SEQ ID NO:57) was expressly disclosed as one of a finite number of efficient exon 53 skipping oligonucleotides. As such, any one of Watanabe's efficient oligonucleotides including SEQ ID NO:57 was available to a person of ordinary skill in the art to make an exon 53 skipping oligonucleotide. In addition, Watanabe's SEQ ID NO:57 showed "higher activity" in exon 53 skipping as shown in Figures 9 and 13. As such, there is no sufficient reason not to select SEQ ID NO:57 for PMO and 5'-PEG conjugate modifications, wherein the two combination modifications were "identified, predictable solutions" available in the relevant art when making an exon skipping oligonucleotide as evidenced by Watanabe's

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teaching of exon skipping oligonucleotides comprising both PMO and the 5' PEG conjugate structure as represented by chemical formula (1) claimed in claim 8 as copied below:



Applicant argues that Watanabe shows four oligonucleotides that are “more effective” than SEQ ID NO:57 by pointing out Figure 17 hence the four oligonucleotides “would have been more promising than” SEQ ID NO:57. In response, the mere fact that there are other oligonucleotides that provided more efficient exon 53 skipping than SEQ ID NO:57 does not whatsoever indicate that one of ordinary skill in the art was taught away or discouraged from using the very effective SEQ ID NO:57. The mere presence of other options does not render the instant claims nonobvious because any one of Watanabe’s oligonucleotides shown to have exon 53 skipping activity (thus including SEQ ID NO:57 and four oligonucleotides that are more efficient than SEQ ID NO:57) would have been a natural compound to be selected when making an exon 53 skipping oligonucleotide modified with the well-known, art-recognized PMO and the 5'-PEG conjugate modifications. Put it differently, all of efficient oligonucleotides showing exon skipping activity in Figure 17 are suitable candidates for making a PMO oligonucleotide. Hence, one of ordinary skill in the art would have modified SEQ ID NO:57 as well as all other oligonucleotide having exon skipping efficiency, thereby rendering the claimed compound *prima facie* obvious.

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Applicant argues even if Watanabe's SEQ ID NO:57 was selected, there is no reason or motivation to replace Watanabe's uracil with thymine. In response, applicant's attention is directed to the fact that the obviousness analysis utilizes a person of ordinary skill in the relevant art, not any layperson. It is *prima facie* obvious knowledge in the relevant art that PMO conventionally utilizes DNA bases as evidenced by Watanabe's teaching of making PMOs comprising SEQ ID NO:2-37 (see paragraphs 0026-0030), all of which are DNA sequences listed in Table 1. As such, there is no technical difficulty or unpredictability involved in utilizing a DNA sequence corresponding to Watanabe's RNA sequence of SEQ ID NO:57 when making a PMO.

Applicant argues that Watanabe does not teach replacing 2'-O-methyl modification in SEQ ID NO:57 with PMO. Contrary to applicant's argument, Watanabe taught that DMD exon 53 skipping oligonucleotides can be in the form of a PMO or a 2'-O-methyl oligomer, thereby providing two chemical modification options when making a DMD exon 53 skipping oligonucleotide. Note that all of Watanabe's oligonucleotides either PMO-modified (see Figure 18) or 2'-O-methyl-modified (see paragraph 0286 and Figures 9 and 13). As such, Watanabe expressly taught only two possible exon skipping oligonucleotide formats: PMO and 2'-O-methyl. Further, the instantly claimed 5' PEG terminal conjugate is one of three 5' end structures (formulas (1)-(3) in claim 8) when making a PMO. Hence, one of ordinary skill in the art properly reading the Watanabe reference would readily understand that PMO and 2'-O-methyl are alternative oligonucleotide formats when making exon skipping oligonucleotides, and since there were only two identified exon skipping formats taught by Watanabe, who also taught three identified 5' end structures for a PMO, a person of ordinary skill in the art would have reasonably pursued making a 5'-PEG conjugated PMO as an obvious alternative approach when making a DMD exon 53 skipping oligonucleotide, wherein the person would have had

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reasonably selected SEQ ID NO:57 because it demonstrated high exon skipping efficiency (about 80%-90%) as demonstrated in Figures 9, 13, and 17.

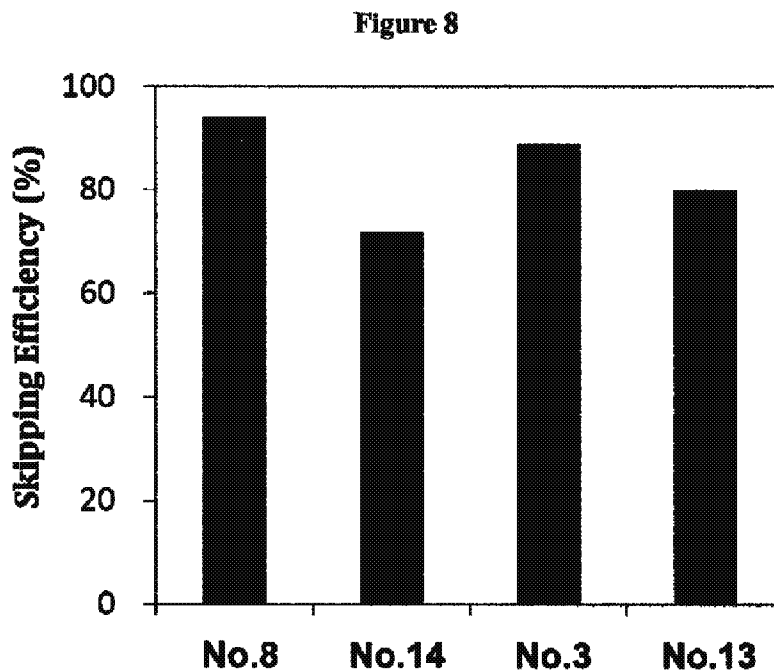
Applicant argues that there is no motivation to use Watanabe's Group (1), the PEG conjugate, because Watanabe indicated that Group (3) is "preferred" among Group (1), Group (2), and Group (3) by pointing out paragraph 0162, which states that "the 5' end may be any of chemical structures (1) to (3) below, and preferably is (3)-OH." In response, the phrase "preferably is (3)-OH" does not teach or suggest that Group (3) alone should be used when making exon skipping PMOs, nor does the phrase teach that Group (1) should not be used. It is clear from the disclosure in paragraph 0162 that Groups (1)-(3) are alternative structures as Watanabe teaches that the 5' end "may be **any** of chemical structures (1) to (3)". It becomes even clearer that the three 5' end structures are alternatives and "any" one of Groups (1)-(3) can be used when Watanabe's claim 8 that expressly recites "wherein the 5' end **is any one** of the groups of chemical formulae (1) to (3)" is taken into consideration. Note that there is no teaching in Watanabe that disparages use of Group (1), and if such were the case, Watanabe would not have claimed Group (1) as one of 5' end group. In addition, note that the mere word "preferably" does not teach away from using Group (1) thus does not render allegedly non-preferred compounds (e.g., Group (1) and Group (2)) nonobvious. See MPEP §2123: "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments."

Applicant argues that one of ordinary skill in the art would have selected Group (3) but not Group (1) by comparing PMOs 3 and 8 having Group (3) to PMOs 13 and 14 having Group (1) and by pointing out that other prior art used Group (3), not Group (1). Applicant goes even further to allege that the examiner's rejection based on the use of Group (1) "contradicts the teachings of Watanabe." Contrary to applicant's arguments and allegations, there is no sufficient reason that one of ordinary skill in the art would not select Group (1) as alleged by applicant

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because PMOs 13 and 14 provided good/high levels (70-80%) of exon 53 skipping efficiency as clearly demonstrated in Figure 8 copied below:



There is nothing in Watanabe including paragraphs 0162 and 0313 pointed out by applicant that clearly criticizes or disparages use of Group (1) at the 5' end when making an exon 53 skipping PMO. Again, Watanabe expressly taught “any” one of Group (1), Group (2), and Group (3) “is” the 5' end group (see claim 8) and furthermore demonstrated that PMOs having Group (1) provided good/high levels (70-80%) of exon 53 skipping efficiency thus use of Group (1) was not discouraged by Watanabe’s teachings. As such, use of Group (1) does not contradict Watanabe’s teachings. Rather, use of Group (1) at the 5' end of a PMO well reflects and is in line with Watanabe’s teachings as Watanabe taught “any” one of Group (1), Group (2), and Group (3) is used as the 5' end group and further exemplified actual use of Group (1).

“A known or **obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product** for the same use.” *In re Gurley* (27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). (emphasis added).

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“A reference does not teach away, however, if it merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed.” *Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327, 90 USPQ2d 1865 (Fed. Cir. 2009). (emphasis added).

In view of the foregoing, this rejection is maintained.

Claims 16-17 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Popplewell et al. in view of Watanabe et al. for the reasons of record as set forth in the Office action mailed on February 28, 2017 and for the reasons set forth below.

Applicant's arguments filed on August 28, 2017 have been fully considered but they are not persuasive. Applicant argues there is no motivation to select SEQ ID NO:22 as a lead compound for modification. In response, it is noted that there is no *per se* rule that requires a selection of a single lead compound for obviousness under §103. See MPEP §2143: The Federal Circuit in *Eisai* makes it clear that from the perspective of the law of obviousness, **any known compound might possibly serve as a lead compound...**It should be noted that the **lead compound cases do not stand for the proposition that identification of a single lead compound is necessary in every obviousness rejection of a chemical compound.**” (emphasis added).

Applicant argues Popplewell's disclosure includes “millions of different possible molecules” thus the “scope” within SEQ ID NOs:1-12 is “vast.” In response to applicant's illogical arguments, Popplewell's SEQ ID NO:10 (a 30-mer sequence wherein X can be U or T) that is expressly taught to be amenable to being shortened to a 25-mer, 26-mer, 27-mer, 28-mer, and 29-mer does not encompass applicant's alleged “millions of different possible molecules” even if Popplewell's paragraph 0031 pointed out by applicant is considered, thus the species encompassed by Popplewell's SEQ ID NO:10 is not “vast.” Applicant's arguments are so fallible

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and incongruent because there is no reason to count the numbers of species for all SEQ ID NOs:1-12 because three nucleotide sequences (SEQ ID NOs:10, 11, and 12) are the only sequences for skipping exon 53. Note that SEQ ID NOs:1-9 do not relate to skipping exon 53. As such, applicant's exaggerated arguments do not support applicant's allegation. The examiner fails to understand why applicant continues to exemplify SEQ ID NO:1 that skips exon 44.

Applicant proposes that one of ordinary skill in the art would rather choose SEQ ID NO:21, which was "superior" to other molecules including SEQ ID NO:22. In response, applicant's proposed idea does not support the alleged nonobviousness of the claims because there is no legal requirement that the selected molecule for modification must be superior to other species in the cited art.

"A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley* (27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). (emphasis added).

Further, the mere fact that SEQ ID NO:21 was found superior to SEQ ID NO:22 does not provide any evidence that one of ordinary skill was taught away from making a 25-mer based on SEQ ID NO:22.

Furthermore, applicant's attention is directed to the fact that Popplewell's SEQ ID NO:21 is not targeted to exon 53. SEQ ID NO:21 is designed to skip exon 46. Hence, the examiner fails to understand applicant's argument regarding SEQ ID NO:21.

Applicant then presents another line of reasoning for not selecting SEQ ID NO:22 by pointing out that Watanabe selected SEQ ID NO:21 "from all the possible molecules of Popplewell". In arguing so, applicant points out Watanabe's Table 2 containing 16 PMOs, wherein PMO 12 and PMO 15 correspond to SEQ ID NO:21. Applicant's attention is directed to the fact that there is no disclosure in the Watanabe's publication that SEQ ID NO:21 was indeed selected "from all the possible molecules of Popplewell". Further, as noted above, Popplewell's

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SEQ ID NO:21 is for skipping exon 46 thus irrelevant to the instantly claimed subject matter as well as the instant ground of rejection.

For the sake of argument, Popplewell's SEQ ID NO:21 pointed out by applicant will be interpreted as SEQ ID NO:24. Now, applicant's attention is directed to the fact that the Popplewell's NPL (*Neuromuscular Disorders*, 2010) mentioned in the Watanabe's publication and also in applicant's remarks clearly and unambiguously shows that SEQ ID NO:22 targeted to "H53A30/2" ("PMO-H") is more efficient in exon 53 skipping (87.2%) than applicant's proposed selection of SEQ ID NO:24 targeted to "H53A30/1" ("PMO-G") providing 52.4% skipping in normal muscle cells. See Table 1 of the 2010 reference. See also Figure 1 of the 2010 reference demonstrating that there is no significant difference between "H53A30/2" ("PMO-H") and "H53A30/1" ("PMO-G") in exon 53 skipping activity in DMD muscle cells. See also Figure 1 legend: "PMO-G gave significantly higher efficacy of exon skipping than PMOs C, D, E, F, J, K and L ($p < 0.005$), **but not significantly higher than PMOs A, B, H, I and M.**" (emphasis added). Most important, there is no evidential basis that Watanabe purposefully selected "H53A30/1" over "H53A30/2" "from all the possible molecules of Popplewell" because "H53A30/2" is deemed unsuitable or undesirable. There is no teaching-away evidence that a relevant artisan would not have selected Popplewell's SEQ ID NO:22 and make a 25-mer consisting of the instantly claimed sequence. Applicant's attention is also directed to Popplewell's paragraph 0086 expressly disclosing that SEQ ID NO:22 (also referred to as "PMO-H") provided efficient exon 53 skipping in muscle cells such that "at 300 nM, PMO-G and **PMO-H gave over 80% skipping of exon 53** (data not shown)." (emphasis added). See also paragraph 0087 disclosing that PMO-H provided efficient exon 53 skipping in DMD patient muscle cells such that "PMO-G, **PMO-H** and PMO-A were **most active producing in the order of 60% exon skipping** (FIG.8)." (emphasis added). As such, applicant's various attempts to undermine Popplewell's SEQ ID NO:22 are found spurious and unpersuasive.

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Applicant asserts that there is no reason to shorten Popplewell's SEQ ID NO:22 because a 25-mer exhibited "poor" exon skipping activity compared to a 30-mer thus Popplewell "teaches away" from making a 25-mer. Contrary to applicant's assertions, there is no express teaching-away disclosure that a 25-mer should not be synthesized. If such were the case, Popplewell would not have claimed at least a 25-mer length of SEQ ID NO:22. In addition, the mere fact that a 25-mer showed a lower level of exon skipping than a 30-mer does not clearly discourage or disparage making a 25-mer PMO. Again, note that "A known or **obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product** for the same use." *In re Gurley* (27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). (emphasis added). Also note that "A reference **does not teach away, however, if it merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed.**" *Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327, 90 USPQ2d 1865 (Fed. Cir. 2009). (emphasis added).

In the instant case, there is no express criticism or discouragement in the Popplewell reference regarding making a 25-mer PMO, even if applicant's assertion that a 30-mer performs better thus Popplewell implicitly expressed "a general preference" for a 30-mer PMO is fully taken into consideration. Again, if Popplewell indeed expressly taught away from making a 25-mer, Popplewell would not have described making a 25-mer in the specification, nor would have claimed a 25-mer PMO in the patent application publication.

In fact, Popplewell synthesized and tested a 25-mer (targeted to positions +35+59) referred to as "PMO-A" that is shortened from SEQ ID NO:22 (positions +33+62). Now, note that Popplewell taught "PMO-A" showed exon skipping activity in normal muscle cells such that "**higher levels of exon skipping were observed for PMO-A and PMO-B only, with 300 nM doses producing 41.2% and 34.3% exon skipping, respectively.**" (emphasis added). See

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paragraph 0085. Further, Popplewell taught that PMO-A produced long-lasting exon skipping of over 60% in DMD patient cells. See paragraph 0088: “The exon skipping produced by the six most bioactive PMOs was shown to be persistent, lasting for up to 10 days after transfection, with **over 60% exon skipping observed for the lifetime of the cultures for PMO-A, PMO-G and PMO-H** (FIG. 10a, b). **Exon skipping was shown to persist for 21 days for PMO-A and PMO-G** (FIG. 10c).” (emphasis added). Hence, applicant’s spurious arguments addressing non-exon 53 skipping oligonucleotides and variable levels of exon skipping do not whatsoever rebut the objective facts/disclosures regarding the long-lasting, effective exon skipping activity of the 25-mer (“PMO-A”) taught, claimed, and disclosed by Popplewell, wherein the 25-mer is designed/truncated from SEQ ID NO:22.

The examiner fails to understand applicant’s arguments addressing PMO-B (see pages 25 and 27). Note that the instant rejection is based on the 25-mer sequence targeted to positions +36+60 encompassed by SEQ ID NO:22 (positions +33+62), wherein PMO-A targeted to +35+59 is strikingly similar to the instantly claimed sequence by only 1 nucleotide shift, whereas PMO-B targeted to +38+62 differs from the claimed sequence by 2 nucleotide shift. Now, note that Popplewell expressly taught that “**higher levels of exon skipping were observed for PMO-A and PMO-B only**, with 300 nM doses producing 41.2% and 34.3% exon skipping, respectively.” (emphasis added). See paragraph 0085. Further, Popplewell described PMO-A and PMO-B as “the **most bioactive 25mers (PMO-A and PMO-B)**” (emphasis added). See paragraph 0089. As such, Popplewell expressly taught 25-mer POMs designed based on SEQ ID NO:22, wherein the 25-mers have only 1-2 nucleotide shift from the 25-mer rendered obvious in the instant rejection are deemed active in providing exon skipping. As such, applicant’s arguments regarding “unpredictable” nature of AONs by addressing non-exon 53 skipping oligonucleotides and the less exon skipping activity by PMO-A and PMO-B compared to 30-mer (e.g., PMO-H; SEQ ID NO:22) are not sufficient to show teaching-away or lack of reasonable

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expectation of success. Further, applicant's argument addressing various levels of exon 53 skipping is not sufficient to rebut the instant obviousness rejection because the variability is not the same as unpredictability. In addition, note that "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 [82 USPQ2d 1321] (Fed. Cir. 2007).

Applicant argues one skilled in the art would not have modified the 5' end of Popplewell's PMO by incorporating Watanabe's PEG conjugate. Applicant then suggests her own idea that one skilled in the art would have incorporated Watanabe's Group (2) or Group (3) modification, not the PEG modification. In response, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Applicant argues Popplewell used "Gene Tools LLC", which utilizes Watanabe's Group (2) modification, not the PEG modification and Popplewell does not teach modifying the existing 5' modification. In response, applicant cannot attack a single reference to show nonobviousness of a claimed feature when a combination of references is used to render the claimed feature obvious. That is, applicant cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Now, the fact that Popplewell's PMO did not have the instantly claimed 5'-PEG conjugate is not sufficient to render the instantly claimed 5'-PEG conjugate nonobvious, because Watanabe taught three identified 5' end structures that are suitable to be utilized when making an exon skipping PMO. Since a finite number (only three) of suitable, alternative 5' modifications for an exon skipping PMO were identified and known in the art, a person of ordinary skill in the

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art would have reasonably pursued making a 5'-PEG (Watanabe's Group (I)) conjugated PMO as an obvious alternative approach to Popplewell's PMO comprising Watanabe's Group (II), wherein the fact that Popplewell's PMO comprises one of Watanabe's three 5' groups reasonably suggests that Watanabe's three 5' groups were in fact a finite number of art-recognized, alternative 5' groups when making an exon skipping PMO.

In view of the foregoing, this rejection is maintained.

Claims 16-17 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sazani et al. in view of Watanabe et al. for the reasons of record as set forth in the Office action mailed on February 28, 2017 and for the reasons set forth below.

Applicant's arguments filed on August 28, 2017 have been fully considered but they are not persuasive. Applicant's repeated "lead compound" argument is not found persuasive. Note that there is no *per se* rule that requires a selection of a single lead compound for obviousness under §103. Applicant argues that one of ordinary skill in the art would be "discouraged" from shortening SEQ ID NO:631 to a 25-mer "based on the teachings of Popplewell discussed above." The examiner fails to understand why Popplewell's teachings are relevant to the instant rejection. Sazani is a completely independent and different from Popplewell, and the instant rejection is not based on Popplewell. Further, there is no teaching in Sazani that refers to Popplewell's '212 publication. Furthermore, even if one should consider Popplewell for the instant rejection, there is no teaching whatsoever in Popplewell that clearly "discourages" one of ordinary skill in the art from making a 25-mer based on the effective 30-mer sequence as amply explained hereinabove. In addition, applicant's attention is directed to the fact that a reference does not teach away unless there is an express discouragement.

"A reference does not teach away, however, if it merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise

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discourage investigation into the invention claimed.” *Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327, 90 USPQ2d 1865 (Fed. Cir. 2009). (emphasis added).

Applicant argues one skilled in the art would utilize Watanabe’s Group (3) instead of Group (1). In response, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Applicant argues there is no reasonable expectation of success “for all the reasons already discussed above.” If applicant is referring to the arguments addressed in the previous rejections, it is noted that applicant’s arguments are not found persuasive for the same reasons set forth hereinabove, which are fully incorporated by reference herein.

In view of the foregoing, this rejection is maintained.

Claims 16-17 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wilton et al. in view of Watanabe et al. for the reasons of record as set forth in the Office action mailed on February 28, 2017 and for the reasons set forth below.

Applicant's arguments filed on August 28, 2017 have been fully considered but they are not persuasive. Applicant’s repeated “lead compound” argument is not found persuasive. Note that there is no *per se* rule that requires a selection of a single lead compound for obviousness under §103. Applicant provides spurious arguments stating that Watanabe selected Wilton’s SEQ ID NO:193, which is a 31-mer. Applicant’s attention is directed to the fact that the mere fact that Watanabe included Wilton’s SEQ ID NO:193 in Table 2 does not whatsoever teach, let alone suggest, that Wilton’s SEQ ID NO:193 cannot be shortened to a 25-mer or that Wilton’s SEQ ID NO:193 was prohibited from being truncated to a 25-mer. In addition, applicant’s attention is directed to the fact that Watanabe taught making an exon 53 skipping oligonucleotide targeted to

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positions +36+60, which are the same positions targeted by the oligonucleotide sequence encompassed by Wilton's claims and by applicant's claims. See the anticipation and obviousness rejections over Watanabe's '062 publication. Applicant's spurious and illogical argument addressing Watanabe's use of the full 31-mer cannot nullify the objective fact that Wilton claimed a 25-mer comprising at least "20 consecutive bases" of SEQ ID NO:193 for exon 53 skipping.

Applicant argues there is no reason to add three bases to arrive at the claimed 25-mer sequence. In response, it is noted that the nucleotide sequence limitation as claimed in Wilton's claims does read on the instantly claimed nucleotide sequence. There is no reason/motivation needed in order to arrive at the claimed nucleotide sequence. One of ordinary skill in the art reading and interpreting Wilton's claims would readily understand that the instantly claimed nucleotide sequence reads on Wilton's claimed nucleotide sequences.

Applicant argues one skilled in the art would utilize Watanabe's Group (3) instead of Group (1) and Wilton's SEQ ID NO:193 has Group (3). In response, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Note that applicant did not provide any persuasive rebuttal arguments as to why one skilled in the art would not utilize Watanabe's Group (1) hence failed to properly rebut the instant rejection.

Applicant generally alleges, without any specific, objective evidence, that "there was a significant level of unpredictability associated with selecting specific AONs to induce effective exon skipping of human dystrophin pre-mRNA at the time of the invention." Note that the instantly claimed 25-mer sequence reads on Wilton's claims thus there is no "significant level of unpredictability" regarding the claimed PMO nucleotide sequence.

In view of the foregoing, this rejection is maintained.

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Double Patenting

Claims 16-17 remain provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-2, 5-35, 39, and 42 of Application No. 15/417,401 for the reasons of record as set forth in the Office action mailed on February 28, 2017 because applicant did not provide any substantially rebuttal arguments.

Claims 16-17 remain provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22, 24, and 27 of Application No. 15/420,823 for the reasons of record as set forth in the Office action mailed on February 28, 2017 because applicant did not provide any substantially rebuttal arguments.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA H SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday-Thursday: 8am - 6:30pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, RAM SHUKLA can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DANA H SHIN/
Primary Examiner, Art Unit 1674



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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			ART UNIT	PAPER NUMBER
			1674	
			NOTIFICATION DATE	DELIVERY MODE
			01/05/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Application No.

15/359,152

Applicant(s)

KAYE, Edward M.

Office Action Summary

Examiner

EKATERINA POLIAKOVA

Art Unit

1674

AIA Status

No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 22 November 2016

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____

2a) ☐ This action is **FINAL**.

2b) ☒ This action is non-final.

3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☒ Claim(s) 1-23 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☒ Claim(s) 1-23 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10) ☐ The specification is objected to by the Examiner.

11) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some** c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

3) ☐ Interview Summary (PTO-413)

Paper No(s)/Mail Date _____

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)

4) ☐ Other: _____

Paper No(s)/Mail Date _____

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DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Claim Objections

Claim 19 is objected to because of the following informalities: each of these claims contains a limitation that refers to one or more Tables. MPEP 2173.05(s) states in part:

Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim.

In the instant case, Tables 3 and 4 are referred to for the purpose of claiming nucleotide sequences, which can be easily incorporated into the claims by reference to SEQ ID NOs.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of 35 U.S.C. 112(b):

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8 and 10 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

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The term "substantially uncharged" in claims 8 and 10 is a relative term which renders the claims indefinite. The term "substantially uncharged" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Paragraph [0095] of instant specification defines how such substantially uncharged oligonucleotide can be modified, but there is no definition how substantially uncharged oligonucleotide is different from uncharged oligonucleotide.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim(s) 1-11, 14-19, 21-23 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Clinical Trial NCT01396239 (ClinicalTrials.gov, published online on 07/15/2011, 4 pages, cited from IDS) as evidenced by Sazani et al (International Journal of Toxicology, 2010, No. 26, 2: 143-156).

Clinical Trial NCT01396239 discloses a method for treating Duchenne muscular dystrophy through induction of dystrophin expression by administration of eteplirsen (same as AVI-4658 and as instant SEQ ID NO: 1) in 50 mg/kg or 30 mg/kg dosing (see page 1) once weekly by single intravenous (i.v.) infusion to patients of 7 to 13 years old, having an out-of-frame deletion(s) that may be corrected by skipping exon 51 (see page 2), who receive treatment with

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oral corticosteroid for at least 24 weeks before eteplirsen treatment (see first paragraph on page 3). Sazani et al disclose that AVI-4658 or eteplirsen (see second column on page 144), identical to instant SEQ ID NO: 1, is substantially uncharged antisense oligonucleotide containing phosphorodiamidate morpholino modifications (see last paragraph in first column on page 144 and Figure 1), which satisfies structural requirements of instant claims 8-11.

Because Clinical Trial NCT01396239 discloses a method of treating Duchenne muscular dystrophy by eteplirsen, which satisfies structural requirements of claim 1, the outcomes listed in dependent claims 2-4 and 7 are expected to happen in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-23 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Clinical Trial NCT01396239, above, and in further view of Sazani et al-2 (US 2010/0130591, May 2010, cited from IDS) and Sazani et al, above.

Teaching of Clinical Trial NCT01396239 are discussed above.

Clinical Trial NCT01396239 do not teach oligonucleotide delivery by conjugation to arginine-rich peptide or delivery in phosphate-buffered saline.

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Sazani et al-2 teach that delivery of eteplirsen (SEQ ID NO: 588) can be improved by its conjugation to arginine-rich peptide to enhance transport to the target cell (see paragraph [0178]).

Sazani et al teach delivery of eteplirsen in phosphate-buffered saline (see Table I on page 146).

It would have been obvious to one of the ordinary skill in the art at the time of the invention to improve method of treating Duchenne muscular dystrophy by administering eteplirsen conjugated to arginine-rich peptide and in phosphate-buffered saline based on teachings of Clinical Trial NCT01396239, Sazani et al-2 and Sazani et al. One of the ordinary skill in the art would be motivated to do so to improve delivery of the oligonucleotide to target cell as taught by Sazani et al-2 and to use phosphate-buffered saline as such adjuvant was appropriate for eteplirsen delivery as taught by Sazani et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed.

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Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(I)(1) - 706.02(I)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1-23 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-29 of U.S. Patent No. 9,506,058. Although the claims at issue are not identical, they are not patentably distinct from each other because claims from '058 cover

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overlapping subject matter with instant claims, treating the same disease with the same compound, eteplirsen, at the same dosage, therefore claims of '058 anticipate instant claims.

Claims 1-23 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of copending Application No. 15/604,335 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because they cover overlapping subject matter, treating the same disease with eteplirsen of the same dosage, therefore claim 1 from '335 anticipates instant claims.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to EKATERINA POLIAKOVA whose telephone number is (571)270-5257. The examiner can normally be reached on Mon-Fri 8-5.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571)272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/EKATERINA POLIAKOVA-GEORGANTAS/
Primary Examiner, Art Unit 1674



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/417,401	01/27/2017	Richard K. BESTWICK	AVN-017CN	3857
123147	7590	10/12/2017	EXAMINER	
Nelson Mullins Riley & Scarborough LLP/Sarepta One Post Office Square Boston, MA 02109			SHIN, DANA H	
			ART UNIT	PAPER NUMBER
			1674	
			NOTIFICATION DATE	DELIVERY MODE
			10/12/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

Application No.

15/417,401

Applicant(s)

BESTWICK et al.

Office Action Summary

Examiner

DANA H SHIN

Art Unit

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AIA Status

No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 September 2017.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

- 5) ☒ Claim(s) 1-3,7-8,11-12,15-16,18-19,24-25,28-29,32-33,35 and 39-40 is/are pending in the application.
5a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 6) ☐ Claim(s) _____ is/are allowed.
- 7) ☒ Claim(s) 1-3,7-8,11-12,15-16,18-19,24-25,28-29,32-33,35 and 39-40 is/are rejected.
- 8) ☐ Claim(s) _____ is/are objected to.
- 9) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

- 10) ☒ The specification is objected to by the Examiner.
- 11) ☒ The drawing(s) filed on 27 January 2017 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some** c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date _____.
- 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____.
- 4) ☐ Other: _____.

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DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Status of Claims

Claims 1-3, 7-8, 11-12, 15-16, 18-19, 24-25, 28-29, 32-33, 35, and 39-40 are currently pending and under examination on the merits in the instant case.

Drawings

It is noted that Figure 2 contains a drawing in red color. See the PDF file filed on January 27, 2017.

Color photographs and color drawings are not accepted in utility applications unless a petition filed under 37 CFR 1.84(a)(2) is granted. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), one set of color drawings or color photographs, as appropriate, if submitted via EFS-Web or three sets of color drawings or color photographs, as appropriate, if not submitted via EFS-Web, and, unless already present, an amendment to include the following language as the first paragraph of the brief description of the drawings section of the specification:

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings and black and white photographs have been satisfied. See 37 CFR 1.84(b)(2).

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Specification

The disclosure is objected to for containing sequence rule non-compliant subject matter. See Figure 2 showing a nucleotide sequence immediately below “Exon53”. Either the Figure or the description of the Figure must identify the nucleotide sequence with an appropriate SEQ ID NO. If the nucleotide sequence is not included in the sequence listing, applicant is required to correctly update the sequence listing both in paper and CRF. See 37 CFR §§1.821-1.825.

Appropriate correction is required.

The abstract of the disclosure is objected to because it is shorter than 50 words in length. Correction is required. See MPEP § 608.01(b).

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
- (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

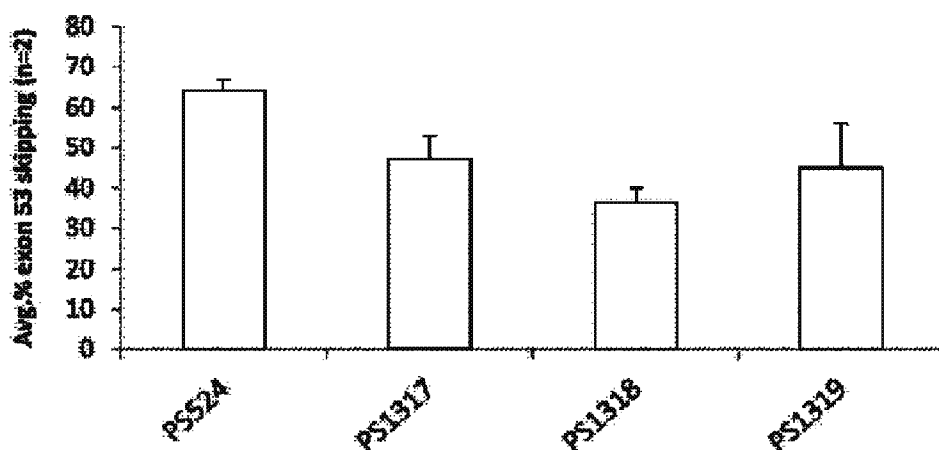
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Claims 1-3, 7-8, 11-12, 15-16, 18-19, 24-25, 28-29, 32-33, 35, and 39-40 are rejected under pre-AIA 35 U.S.C. 102(e) as being anticipated by De Visser et al. (US 2015/0045413 A1, applicant's citation).

De Visser discloses 25-mer antisense oligonucleotides ("PS524", "PS1317", "PS1318", and "PS1319") targeted to exon 53 of human dystrophin, wherein the oligonucleotides comprise 5'-methylcytosine and linked by phosphorothioate backbones, wherein the oligonucleotides have the nucleotide sequence of 5'-GUUGCCUCCGGUUCUGAAGGUGUUC, which corresponds to the RNA equivalent sequence of SEQ ID NO:14 claimed in the instant case. See paragraph 0007 and Figure 1C.

De Visser demonstrates that the oligonucleotides induce exon 53 skipping. See Figure 1C copied below, wherein the underlining in the nucleotide sequences represent 5'-methylcytosine substitution:



AON	Conc. (nM)	Sequence (5'-3')
PS524	400	GUUG <u>CCU</u> CCGGUUCUGAAGGUGUUC
PS1317	400	GUUG <u>CCU</u> CCGGUUCUGAAGGUGUUC
PS1318	400	GUUG <u>CCU</u> CCGGUUCUGAAGGUGUUC
PS1319	400	GUUG <u>CCU</u> CCGGUUCUGAAGGUGUUC

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De Visser teaches that exon skipping oligonucleotides can be PMO oligonucleotides or can comprise peptide nucleic acids. See paragraphs 0046-0047.

De Visser teaches that the oligonucleotides can be linked to a cell targeting/delivery moiety such as polyethylene glycol (PEG). See paragraphs 0642-0643.

De Visser teaches that the exon 53 skipping oligonucleotides can be formulated as a pharmaceutical composition for treating DMD. See paragraphs 0074-0075, 0637, 0649-0650.

Accordingly, claims 1-3, 7-8, 11-12, 15-16, 18-19, 24-25, 28-29, 32-33, 35, and 39-40 are anticipated by De Visser et al.

Claims 1, 7-8, 11-12, 15-16, 18-19, 24-25, 28-29, 32-33, 35, and 39-40 are rejected under pre-AIA 35 U.S.C. 102(e) as being anticipated by Wilton et al. (US 8,232,384 B2, applicant's citation).

Wilton's '384 patent claims an oligonucleotide (SEQ ID NO:195) complementary to H53A (+23+47), wherein the oligonucleotide comprises PMO or a peptide nucleic acid and is conjugated to a polyethylene glycol molecule, wherein the oligonucleotide comprises at least 10 nucleotides of the recited SEQ ID NOs in the instant case. Wilton's 384 patent also claims a method of treating DMD. See claims 1-25.

Accordingly, claims 1, 7-8, 11-12, 15-16, 18-19, 24-25, 28-29, 32-33, 35, and 39-40 are clearly anticipated by the '384 patent claims.

Claims 1-3, 7-8, 11-12, 15-16, 18-19, 24-25, 28-29, 32-33, 35, and 39-40 are rejected under pre-AIA 35 U.S.C. 102(a) and 102(e) as being anticipated by Watanabe et al. (WO 2012/029986 A1, applicant's citation).

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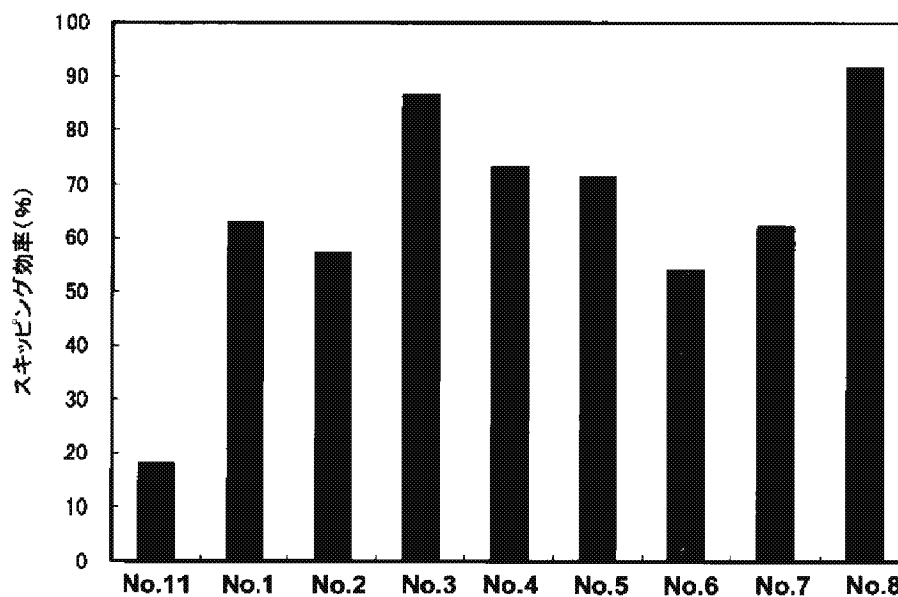
Watanabe discloses a 25-mer antisense oligonucleotide (SEQ ID NO:57) that is complementary to nucleotide positions 36-60 of exon 53 of human dystrophin. See below:

H53_36-60		GUUGCCUCCGGUUCUGAAGGUGUUC		57
------------------	--	----------------------------------	--	-----------

It is noted that the above 25-mer RNA sequence is an RNA equivalent that is 100% identical to SEQ ID NO:14 claimed in the instant case.

Watanabe demonstrates that SEQ ID NO:57 (“H53 36-60”) induces exon 53 skipping to about 80%. See Figure 9. See also Figure 13 showing exon 53 skipping by “H53 36-60”.

Watanabe teaches making PMO oligomers, wherein PMO No. 8 is targeted to nucleotide positions 36-56. See Table 2 at page 28. PMO No. 8 is shown to induce skipping of exon 53. See Figure 1:



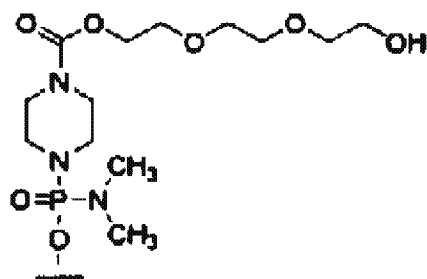
Watanabe teaches that the exon 53 skipping oligonucleotides can be “peptide nucleic acid (PNA) oligomer having a length of 18 to 28 bases”. See paragraph 0005 of the English translation.

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Watanabe teaches that the oligonucleotides that induce skipping of dystrophin exon 53 can be formulated as a pharmaceutical composition and be used in a DMD treatment method. See paragraphs 0002-0003, 0007, and claim 13 of the English translation.

Watanabe teaches that the PMO oligonucleotide is conjugated to a PEG as shown in chemical formula (1) in paragraph 0003 as copied below:



(1)

Accordingly, claims 1-3, 7-8, 11-12, 15-16, 18-19, 24-25, 28-29, 32-33, 35, and 39-40 are anticipated by Watanabe et al.

Claims 1-3, 7-8, 11-12, 16, 18-19, 24-25, 28-29, 33, 35, and 39-40 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Popplewell et al. (US 2010/0168212 A1, applicant's citation).

Popplewell discloses PMO-modified 30-mer antisense oligonucleotides (SEQ ID NOs:22 and 23) targeted to human dystrophin exon 53, wherein the oligonucleotides comprise at least 10 nucleotides of SEQ ID NO:10. See SEQ ID NOs:22-23 as disclosed in paragraph 0055, wherein underlining has been added to indicate nucleotides present in SEQ ID NO:14:

(SEQ ID NO: 22)

H53A30/2 -
CTG TTG CCT CCG GTT CTG AAG GTG TTC TTG;

(SEQ ID NO: 23)

H53A30/3 -
CAA CTG TTG CCT CCG GTT CTG AAG GTG TTC;

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Popplewell teaches that the two oligonucleotides induce about 80% and 87% exon 53 skipping. See Table 1.

Popplewell teaches making a pharmaceutical composition comprising the exon skipping oligonucleotide and a pharmaceutically acceptable carrier (e.g., buffer comprising phosphates) and using the composition for treating DMD, wherein the oligonucleotide can be conjugated to a delivery enhancing agent such as a cell penetrating peptide (CPP) or can be conjugated to polyethylene glycol. See claims 9-12; paragraphs 0033 and 0035.

Popplewell teaches making a PMO oligonucleotide comprising at least 25 nucleotides of SEQ ID NO:11 (5'-CAACTGTTGCCTCCGGTTCTGAAGGTGTTC), wherein the underlined 25-mer is 100% identical to SEQ ID NO:14 claimed in the instant case. See paragraph 0015.

Accordingly, claims 1-3, 7-8, 11-12, 16, 18-19, 24-25, 28-29, 33, 35, and 39-40 are anticipated by Popplewell et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van*

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Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-32 of U.S. Patent No. 8,779,128 B2 in view of Popplewell et al. (US 2010/0168212 A1, applicant's citation).

Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are encompassed by and obvious over the '128 patent claims, which are broadly drawn to any oligomer having a 5'-PEG conjugated PMO oligomer (see for

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instance claims 26, 30-31) binding to a target nucleotide sequence. Although the '128 patent claims do not expressly recite that the target binding oligomer is a human dystrophin exon 53 skipping antisense oligonucleotide sequence, the '128 patent specification makes clear that the claimed "oligomer" reads on an exon skipping oligomer as evidenced by columns 83-84, Example 27, and Figures 5-6 that teach that the claimed oligomer is targeted to dystrophin for exon skipping for DMD treatment purpose. As such, one of ordinary skill in the art trying to determine the scope of "oligomer" claimed in the '128 patent claims by looking into the specification would readily understand the claimed oligomer reads on an exon skipping oligonucleotide. Note that "those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent." See MPEP §804. See also *Pfizer Inc. v. Teva Pharmaceuticals USA Inc.*, 518 F.3d 1353, 86 USPQ2d 1001 (Fed. Cir. 2008), wherein the court expressed the following: "To the extent that Pfizer contends that we may not rely on the teachings of the specification or claims in the '165 patent to reject the claims of the '068 patent, we disagree. See *Geneva*, 349 F.3d at 1386. There is nothing that prevents us from looking to the specification to determine the proper scope of the claims."

Now, it is noted that making a dystrophin exon 53 skipping oligonucleotide comprising SEQ ID NO:14 claimed in the instant case was already known in the art as taught by Popplewell et al. As such, the instantly claimed subject matter is fully encompassed and rendered obvious by the scope of the 5'-PEG-conjugated PMO "oligomer" of the '128 patent claims.

Claims 1-3, 7-8, 11-12, 16, 18-19, 24-25, 28-29, 33, 35, and 39 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 16-17 of copending Application No. 14/776,533 (reference application). Although the claims at issue are

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not identical, they are not patentably distinct from each other because the instant claims are anticipated by the PEG-conjugated PMO antisense oligonucleotide of the '533 claims having the nucleotide sequence of 5'-GTTGCCTCCGGTTCTGAAGGTGTTC, which is 100% identical to SEQ ID NO:14 claimed in the instant case.

Claims 1, 7-8, 11-12, 16, 18-19, 24-25, 28-29, 33, 35, and 39 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 2-3 of copending Application No. 15/274,772 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are anticipated by the PEG-conjugated PMO antisense oligonucleotide of the '772 claims having the nucleotide sequence of SEQ ID NO:193 having thymine bases in place of uridines, wherein SEQ ID NO:193 comprises at least 10 consecutive nucleotides of the instantly claimed SEQ ID NOs such as SEQ ID NO:14.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA H SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday-Thursday: 8am - 6:30pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, RAM SHUKLA can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DANA H SHIN/
Primary Examiner, Art Unit 1674



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/420,823	01/31/2017	Richard K. BESTWICK	AVN-010PCCN2	1062
123147	7590	11/02/2017	EXAMINER	
Nelson Mullins Riley & Scarborough LLP/Sarepta One Post Office Square Boston, MA 02109			BOWMAN, AMY HUDSON	
			ART UNIT	PAPER NUMBER
			1674	
			NOTIFICATION DATE	DELIVERY MODE
			11/02/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

Application No.

15/420,823

Applicant(s)

BESTWICK et al.

Office Action Summary

Examiner

Amy H Bowman

Art Unit

1674

AIA Status

No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 9/14/17.
- ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

- 5) ☒ Claim(s) 1-8,10-11,13-20 and 24-25 is/are pending in the application.
- 5a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 6) ☐ Claim(s) _____ is/are allowed.
- 7) ☐ Claim(s) _____ is/are rejected.
- 8) ☐ Claim(s) _____ is/are objected to.
- 9) ☒ Claim(s) 1-8,10-11,13-20 and 24-25 are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some** c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date _____.
- 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____.
- 4) ☐ Other: _____.

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Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

The office action mailed on 9/28/17 has been vacated.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-8, 10, 11, 13-20, and 24, drawn to an isolated antisense oligonucleotide, classified in C12N 15/113.

II. Claim 25, drawn to a method of treating Duchenne muscular dystrophy, classified in A61K 48/00.

The inventions are distinct, each from the other because of the following reasons:

Inventions of group I is related to the inventions of group II as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the product can be used as a size marker on a gel. The method of treatment can be practiced with an antibody or aptamer. To search for one would not necessarily return art against the other.

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Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and/or examination burden if restriction were not required.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of an invention to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other invention.

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Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

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Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be corrected in compliance with 37 CFR 1.48(a) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. A request to correct inventorship under 37 CFR 1.48(a) must be accompanied by an application data sheet in accordance with 37 CFR 1.76 that identifies each inventor by his or her legal name and by the processing fee required under 37 CFR 1.17(i).

The examiner has required restriction between product or apparatus claims and process claims. Where applicant elects claims directed to the product/apparatus, and all product/apparatus claims are subsequently found allowable, withdrawn process claims that include all the limitations of the allowable product/apparatus claims should be considered for rejoinder. All claims directed to a nonelected process invention must include all the limitations of an allowable product/apparatus claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product/apparatus claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product/apparatus are found allowable, an otherwise proper

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restriction requirement between product/apparatus claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product/apparatus claim will not be rejoined. See MPEP § 821.04.

Additionally, in order for rejoinder to occur, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product/apparatus claims. **Failure to do so may result in no rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy Hudson Bowman whose telephone number is (571)272-0755. The examiner can normally be reached on M-F 8:00am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Application/Control Number: 15/420,823
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Page 7

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/AMY H BOWMAN/
Primary Examiner, Art Unit 1674

SRPT-VYDS-0004911



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/422,127	02/01/2017	Richard K. BESTWICK	AVN-013BCN	3599
123147	7590	11/27/2017		
Nelson Mullins Riley & Scarborough LLP/Sarepta One Post Office Square Boston, MA 02109			EXAMINER SHIN, DANA H	
			ART UNIT	PAPER NUMBER
			1674	
			NOTIFICATION DATE	DELIVERY MODE
			11/27/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

Application No.

15/422,127

Applicant(s)

BESTWICK et al.

Office Action Summary

Examiner

DANA H SHIN

Art Unit

1674

AIA Status

No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 15 September 2017

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____

2a) ☐ This action is **FINAL**.

2b) ☒ This action is non-final.

3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☒ Claim(s) 1-2,8-9,16 and 21-57 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☒ Claim(s) 1-2,8-9,16 and 21-57 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10) ☒ The specification is objected to by the Examiner.

11) ☒ The drawing(s) filed on 01 February 2017 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some** c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

3) ☐ Interview Summary (PTO-413)

Paper No(s)/Mail Date _____

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)

4) ☐ Other: _____

Paper No(s)/Mail Date _____

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DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Status of Claims

Claims 1-2, 8-9, 16, and 21-57 are currently pending and under examination on the merits in the instant case.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The abstract is objected to because it is shorter than 50 words in length.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 8-9, 21-22, 30-33, 35-36, 44-47, and 49-50 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Sazani et al. (US 2010/0130591 A1, applicant's citation).

Sazani claims a PMO antisense compound of 20-35 nucleotides in length comprising
SEQ ID NO:4.

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See claim 1 as copied below:

1. A composition for use in producing skipping of exon 44 in the processing of human dystrophin pre-processed mRNA, comprising

a substantially uncharged antisense compound containing 20-35 morpholino subunits linked by phosphorus-containing intersubunit linkages joining a morpholino nitrogen of one subunit to a 5' exocyclic carbon of an adjacent subunit, comprising a sequence selected from the group consisting SEQ ID NOS: 1-20, and capable of forming with the complementary mRNA sequence in the dystrophin-gene exon 44, a heteroduplex structure between said compound and mRNA having a T_m of at least 45° C.

See SEQ ID NO:4 copied below, wherein the underlining indicates the 22-mer claimed in the instant case.

Hu.DMD.Exon44.25.004 GATCTGTCAAATCGCCTGCAGGTAA

4

Since one of ordinary skill in the art can readily envision four 22-mer PMO oligonucleotides within SEQ ID NO:4, wherein one of which is the underlined 22-mer sequence above that is 100% identical to the instantly claimed 22-mer oligonucleotide sequence, the instantly claimed nucleotide sequence of SEQ ID NO:5 is taught by Sazani.

Sazani teaches that “Ts and Us are interchangeable.” See paragraph 0098.

Sazani teaches that the PMO oligonucleotide can be chemically linked to a 5' delivery conjugate via a piperazinyl moiety, wherein the conjugate includes a PEG. See paragraph 0197; Figure 1B.

Sazani teaches making a pharmaceutical composition comprising the PMO oligonucleotide and a pharmaceutically acceptable carrier. See paragraph 0191.

Accordingly, claims 1-2, 8-9, 21-22, 30-33, 35-36, 44-47, and 49-50 are taught by Sazani et al.

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Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 1-2, 8-9, 16, and 21-57 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Sazani et al. (US 2010/0130591 A1, applicant's citation) in view of Hanson (US 2012/0289457 A1).

Sazani claims a PMO antisense compound of 20-35 nucleotides in length comprising SEQ ID NO:4.

See claim 1 as copied below:

1. A composition for use in producing skipping of exon 44 in the processing of human dystrophin pre-processed mRNA, comprising
a substantially uncharged antisense compound containing 20-35 morpholino subunits linked by phosphorus-containing intersubunit linkages joining a morpholino nitrogen of one subunit to a 5' exocyclic carbon of an adjacent subunit, comprising a sequence selected from the group consisting SEQ ID NOS: 1-20, and capable of forming

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with the complementary mRNA sequence in the dystrophin-gene exon 44, a heteroduplex structure between said compound and mRNA having a T_m of at least 45° C.

See SEQ ID NO:4 copied below, wherein the underlining indicates the 22-mer claimed in the instant case.

Hu.DMD.Exon44.25.004 GATCTGTCAAATCGCCTGCAGGTAA

4

Since one of ordinary skill in the art can readily envision four 22-mer PMO oligonucleotides within SEQ ID NO:4, wherein one of which is the underlined 22-mer sequence above that is 100% identical to the instantly claimed 22-mer oligonucleotide sequence, the instantly claimed nucleotide sequence of SEQ ID NO:5 is taught by Sazani.

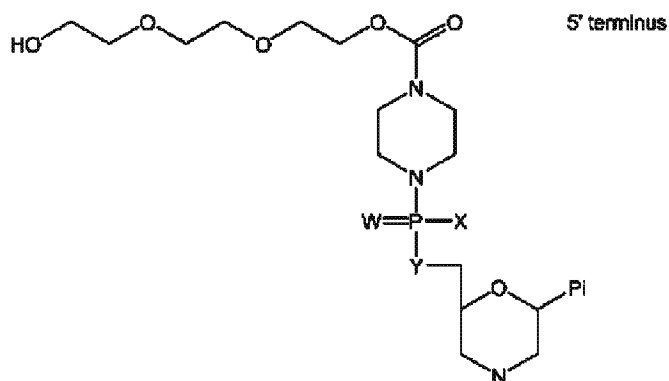
Sazani teaches that “Ts and Us are interchangeable.” See paragraph 0098.

Sazani teaches that the PMO oligonucleotide can be chemically linked to a 5' delivery conjugate via a piperazinyl moiety, wherein the conjugate includes a PEG. See paragraph 0197; Figure 1B.

Sazani teaches making a pharmaceutical composition comprising the PMO oligonucleotide and a pharmaceutically acceptable carrier. See paragraph 0191.

Sazani does not expressly disclose the PEG-linked PMO structure.

Hanson teaches making an exon skipping PMO antisense oligonucleotide comprising a 5' terminus triethylene glycol (“EG3”) linked to the PMO via a piperazine linker as shown in Figure 1C as below:

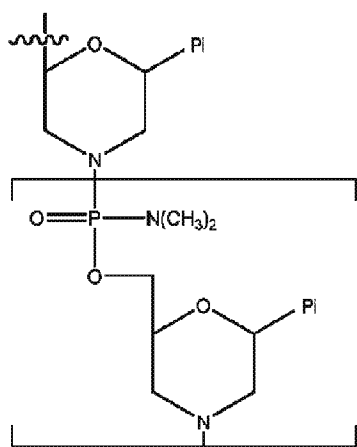


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See also paragraphs 0478-0483; Table 7.

Hanson's above structure has $N(CH_3)_2$ in place of "X" as evidenced by Figure 1A as below:



Hanson also discloses SEQ ID NOs:22, which is identical to Sazani's SEQ ID NO:4. See Table 1 at page 25.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a "EG3"-linked PMO consisting of the first 22-mer sequence of Sazani's SEQ ID NO:4 or Hanson's SEQ ID NO:22. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success because Sazani expressly claimed a PMO of 22 nucleotides of SEQ ID NO:4 (see claim 1), wherein only four 22-mer PMO oligonucleotide sequences are possible when making a 22-mer PMO within Sazani's SEQ ID NO:4 thus arriving at SEQ ID NO:5 would have been *prima facie* obvious, and because PEG-conjugated PMO for skipping DMD exon 44 was taught by Sazani (see paragraph 0197), wherein "EG3"-linked PMO was an art-recognized oligomer design when making an exon skipping oligonucleotides as taught by Hanson.

"When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is

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likely that not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 421, 82 USPQ2d 1385, 1397 (2007).

Accordingly, claims 1-2, 8-9, 16, and 21-57 taken as a whole would have been *prima facie* obvious at the time of the invention.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 2, 24, 31, 38, 45, and 52 are rejected under 35 U.S.C. 101 because the claimed invention is directed to a judicial exception (i.e., a law of nature, a natural phenomenon, or an abstract idea) without significantly more.

The claims are directed to a fragment of a naturally occurring nucleic acid such as human DMD genomic sequence (NG_012232.1). The nucleotide sequence citation is not attached due to the voluminous nature of the nucleotide sequence, which is 2,227,382 nucleotides in length. See instead the nucleotide sequence alignment shown below:

Homo sapiens dystrophin (DMD), RefSeqGene (LRG_199) on chromosome X
Sequence ID: NG_012232.1 Length: 2227382 Number of Matches: 1

Range 1: 1127540 to 1127561 GenBank Graphics				Next Match	Previous Match
Score	Expect	Identities	Gaps	Strand	
44.1 bits(22)	0.017	22/22(100%)	0/22(0%)	Plus/Minus	
Query 1	GATCTGTCAAATCGCCTGCAGG		22		
Sbjct 1127561	GATCTGTCAAATCGCCTGCAGG		1127540		

The claims do not include additional elements that are sufficient to amount to significantly more than the judicial exception because the word “isolated” does not alter the structure of the fragment of a naturally occurring nucleic acid in any way. Further, the intended

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use “pharmaceutical” language in preamble does not structurally alter the fragment of the naturally occurring nucleic acid, and because a pharmaceutically acceptable carrier reads on a salt or sugar solution, which also occurs in nature thus is a natural product.

See Funk Brothers Seed Co. v. Kalo Inoculant Co., U.S. Supreme Court, 333 US127 (1948), wherein the Supreme Court held that the isolated bacteria mixture composition is not patent eligible because the patent holder did not alter the bacteria in any way.

Accordingly, claims 2, 24, 31, 38, 45, and 52 are not patent eligible under §101.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination

Application/Control Number: 15/422,127
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Page9

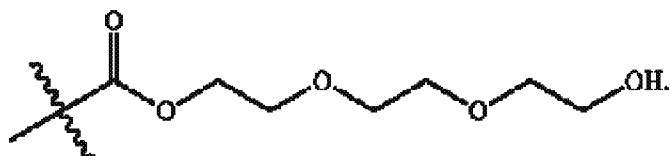
under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1-2, 8-9, 16, and 21-57 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-32 of U.S. Patent No. 8,779,128 B2 in view of Sazani et al. (US 2010/0130591 A1, applicant's citation).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are an obvious variation of and encompassed by the '128 patent claims drawn to a morpholino oligomer having the 5' terminus structure as claimed in claim 30 shown below:

30. The oligomer of claim 26, wherein R¹⁹ is piperiziny1 or



Note that the above structure is identical to the 5' terminus structure claimed in the instant claims.

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Now, the meaning of the “oligomer” claimed in the ‘128 patent claims reads on SEQ ID NO:22 disclosed in Table 11 of the ‘128 patent as below:

Exon44 -A	GATCTGTCAAATCGCCTGCAGGTAA	22
------------------	----------------------------------	-----------

Note that “those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent.” See MPEP §804. See also *Pfizer Inc. v. Teva Pharmaceuticals USA Inc.*, 518 F.3d 1353, 86 USPQ2d 1001 (Fed. Cir. 2008), wherein the court expressed the following: “To the extent that Pfizer contends that we may not rely on the teachings of the specification or claims in the ‘165 patent to reject the claims of the ‘068 patent, we disagree. *See Geneva*, 349 F.3d at 1386. There is nothing that prevents us from looking to the specification to determine the proper scope of the claims.”

It would have been obvious to one of ordinary skill in the art to produce a 3' end-truncated oligonucleotide that is shorter than SEQ ID NO:22 because it is more economical to synthesize shorter oligonucleotides, and because it was known to synthesize dystrophin exon skipping oligonucleotides of 22 nucleotides in length as taught by Sazani (see claim 1).

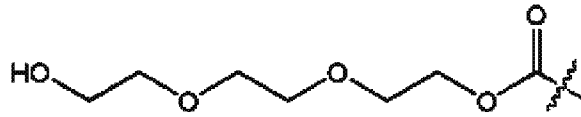
Claims 1-2, 8-9, 16, and 21-57 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 31-32, 35, 39, 44, 46-48, 50-52, 54-55, 65-66, 70, 73-74, 76-77 of copending Application No. 15/247,584 in view of Sazani et al. (US 2010/0130591 A1, applicant’s citation).

Although the conflicting claims are not identical, they are not patentably distinct from other because the instant claims are an obvious variation of and encompassed by the ‘584 claims drawn to a morpholino oligomer having the 5' terminus structure as claimed in claim 74 shown below:

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74. (Original) The oligomer of claim 31, wherein R¹⁹ has the following structure:



Note that the above structure is identical to the 5' terminus structure claimed in the instant claims.

Now, the meaning of the “oligomer” claimed in the ‘584 claims reads on SEQ ID NO:22 disclosed in Table 11 of the ‘584 specification as below:

Exon44-A | GATCTGTCAAATCGCCTGCAGGTAA | 22

Note that “those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent.” See MPEP §804. See also *Pfizer Inc. v. Teva Pharmaceuticals USA Inc.*, 518 F.3d 1353, 86 USPQ2d 1001 (Fed. Cir. 2008), wherein the court expressed the following: “To the extent that Pfizer contends that we may not rely on the teachings of the specification or claims in the ‘165 patent to reject the claims of the ‘068 patent, we disagree. See *Geneva*, 349 F.3d at 1386. There is nothing that prevents us from looking to the specification to determine the proper scope of the claims.”

It would have been obvious to one of ordinary skill in the art to produce a 3' end-truncated oligonucleotide that is shorter than SEQ ID NO:22 because it is more economical to synthesize shorter oligonucleotides, and because it was known to synthesize dystrophin exon skipping oligonucleotides of 22 nucleotides in length as taught by Sazani (see claim 1).

Claims 1-2, 8-9, 16, and 21-57 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-3, 15, 17-20, 32, 34, 38-39, and 43 of copending Application No. 15/431,468, which read on a 22-mer of SEQ ID NO:1 (5'-CAGATCTGTCAAATCGCCTGCAGG), wherein the underlined sequence is 100% identical to

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SEQ ID NO:5 claimed in the instant case. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are anticipated by the '468 claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA H SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday-Thursday: 8am - 6:30pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, RAM SHUKLA can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/DANA H SHIN/
Primary Examiner, Art Unit 1674

37120

Notice of References Cited	Application/Control No. 15/422,127		Applicant(s)/Patent Under Reexamination BESTWICK et al.	
	Examiner DANA H SHIN		Art Unit 1674	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-20120289457-A1	11-2012	Hanson; Gunnar J.	A61K31/713	514/3.1
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

To: chris.schlauch@nelsonmullins.com,ipqualityassuranceboston@nelsonmullins.com,ipboston.docketing@nelsonmullins.com
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 123147

Jan 05, 2018 03:29:01 AM

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Application	Document	Mailroom Date	Attorney Docket No.
15705172	NTC.PUB	01/04/2018	AVN-008CN41

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/705,172	Filing Date 09/14/2017	<input type="checkbox"/> To be Mailed
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ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO**APPLICATION AS FILED – PART I**

(Column 1)

(Column 2)

FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)
<input type="checkbox"/> BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
<input type="checkbox"/> SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
<input type="checkbox"/> EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X \$ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X \$ =	
<input type="checkbox"/> APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

(Column 1)

(Column 2)

(Column 3)

AMENDMENT	01/05/2018	CLAIMS REMAINING AFTER AMENDMENT	MINUS	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
	Total (37 CFR 1.16(i))	* 2	Minus	** 20	= 0	x \$40 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0	x \$210 =	0
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))						
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

(Column 1)

(Column 2)

(Column 3)

AMENDMENT	CLAIMS REMAINING AFTER AMENDMENT	MINUS	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))					
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

SLIE
NICHELE PETERSON

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SRPT-VYDS-0004928

Document Description: Power of Attorney

PTO/AIA/82A (07-13)

Approved for use through 11/30/2014. OMB 0651-0051

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Application Number

15/705,172

Filing Date

September 14, 2017

First Named Inventor

Stephen Donald WILTON

Title

ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND
METHODS OF USE THEREOF

Art Unit

1674

Examiner Name

CHONG, Kimberly

Attorney Docket Number

4140.01500A9

SIGNATURE of Applicant or Patent Practitioner

Signature



Date (Optional)

March 28, 2018

Name

Marsha Rose Gillentine

Registration
Number

58,403

Title (if Applicant is a
juristic entity)

Applicant Name (if Applicant is a juristic entity)

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.



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SRPT-VYDS-0004929

Doc Code: PA..
Document Description: Power of AttorneyPTO/AIA/82B (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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POWER OF ATTORNEY BY APPLICANTI hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date
15/705,172	September 14, 2017

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☒ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above:

153767

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

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153767

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I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

THE UNIVERSITY OF WESTERN AUSTRALIA

☐

Inventor or Joint Inventor (title not required below)

☐

Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

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Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

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Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature

Romy Owens

Date (Optional)

Name

Professor Robyn Owens

Title

Deputy Vice-Chancellor (Research)

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.☒ Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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Electronic Acknowledgement Receipt

EFS ID:	32177928
Application Number:	15705172
International Application Number:	
Confirmation Number:	2879
Title of Invention:	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF
First Named Inventor/Applicant Name:	Stephen Donald WILTON
Customer Number:	123147
Filer:	Marsha Rose Gillentine
Filer Authorized By:	
Attorney Docket Number:	AVN-008CN41
Receipt Date:	28-MAR-2018
Filing Date:	14-SEP-2017
Time Stamp:	16:23:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	4140_01500A9_Filing_POA.pdf	332996 e448cc9f9b39512a8ca09f37e7466c5ba4d6bfb8c	no	2

Warnings:

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New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/705,172	09/14/2017	Stephen Donald WILTON	4140.01500A9

CONFIRMATION NO. 2879

POA ACCEPTANCE LETTER

153767
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005



Date Mailed: 04/02/2018

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 03/28/2018.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at (571) 272-4000 or (571) 272-4200 or 1-888-786-0101.

/nbekele/



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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/705,172	09/14/2017	Stephen Donald WILTON	AVN-008CN41

CONFIRMATION NO. 2879

POWER OF ATTORNEY NOTICE



123147
Nelson Mullins Riley & Scarborough LLP/Sarepta
One Post Office Square
Boston, MA 02109

Date Mailed: 04/02/2018

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

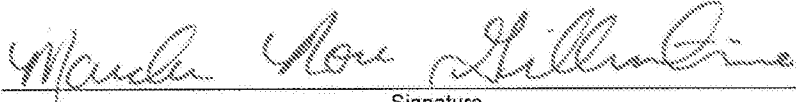
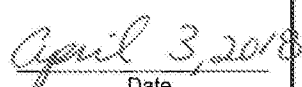
This is in response to the Power of Attorney filed 03/28/2018.

- The Power of Attorney to you in this application has been revoked by the applicant. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at (571) 272-4000 or (571) 272-4200 or 1-888-786-0101.

/nbekele/

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) 4140.01500A9
<p>In re Application of: The University of Western Australia</p> <p>Application No.: 15/705,172</p> <p>Filed: September 14, 2017</p> <p>For: ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF</p> <p>The applicant, <u>The University of Western Australia</u>, owner of <u>100</u> percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent No. <u>8,232,384 B2</u> as the term of said prior patent is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.</p> <p>In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:</p> <ul style="list-style-type: none"> expires for failure to pay a maintenance fee; is held unenforceable; is found invalid by a court of competent jurisdiction; is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321; has all claims canceled by a reexamination certificate; is reissued; or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer. <p>Check either box 1 or 2 below, if appropriate.</p> <p>1. <input type="checkbox"/> The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.</p> <p>I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.</p> <p>2. <input checked="" type="checkbox"/> The undersigned is an attorney or agent of record. Reg. No. <u>58,403</u></p> <div style="text-align: center; margin-top: 20px;">  Signature </div> <div style="text-align: center; margin-top: 20px;">  Date </div> <div style="text-align: center; margin-top: 20px;"> Marsha Rose Gillentine Typed or printed name </div> <div style="display: flex; justify-content: space-between; margin-top: 20px;"> <div style="text-align: center;"> Director Title </div> <div style="text-align: center;"> (202) 371-2600 Telephone Number </div> </div> <p><input checked="" type="checkbox"/> Terminal disclaimer fee under 37 CFR 1.20(d) included.</p> <p style="text-align: center;">WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.</p>	

This collection of information is required by 37 CFR 1.321. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

MARSHA ROSE GILLENTINE
DIRECTOR
(202) 772-8692
MGILLENTINE@STERNEKESSLER.COM



April 3, 2018

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Confirmation No. 2879
Art Unit 1674

Re: U.S. Utility Patent Application
Appl. No. 15/705,172; Filing Date: September 14, 2017
For: **ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON
SKIPPING AND METHODS OF USE THEREOF**
Inventors: WILTON *et al.*
Our Ref: 4140.01500A9

Commissioner:

Transmitted herewith for appropriate action are the following documents:

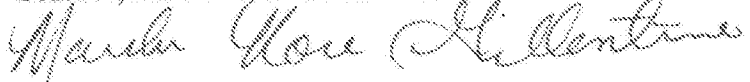
1. Online Credit Card Payment Authorization in the amount of \$160.00 to cover:
\$160.00 – fee for Terminal Disclaimer;
2. Terminal Disclaimer to Obviate a Double Patenting Rejection Over a “Prior” Patent (Form PTO/AIA/26); and
3. Authorization to Treat a Reply as Incorporating an Extension of Time Under 37 C.F.R. § 1.136(a)(3).

The above-listed documents are filed electronically.

In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency and any additional fees required to continue prosecution or appeal of this application (including issue fee, fees for net addition of claims or forwarding to appeal) or credit any overpayment to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.


Marsha Rose Gillentine
Attorney for Applicant
Registration No. 58,403

MRG/NPS:dmc
Enclosures

9204340_1.docx

Electronic Patent Application Fee Transmittal				
Application Number:		15705172		
Filing Date:		14-Sep-2017		
Title of Invention:		ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF		
First Named Inventor/Applicant Name:		Stephen Donald WILTON		
Filer:		Neil P. Shull/Debbie Colonna		
Attorney Docket Number:		4140.01500A9		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

37132

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
Total in USD (\$)				160

Electronic Acknowledgement Receipt

EFS ID:	32231516
Application Number:	15705172
International Application Number:	
Confirmation Number:	2879
Title of Invention:	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF
First Named Inventor/Applicant Name:	Stephen Donald WILTON
Customer Number:	153767
Filer:	Neil P. Shull/Debbie Colonna
Filer Authorized By:	Neil P. Shull
Attorney Docket Number:	4140.01500A9
Receipt Date:	03-APR-2018
Filing Date:	14-SEP-2017
Time Stamp:	14:02:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$ 160
RAM confirmation Number	040418INTEFSW14033300
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		4140_01500A9_Filing_Cover_T D_EOTAuth.pdf	1741910	yes	3
			0d5f119bb5fccbba3ae6f2b261a394c0756a358c		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Authorization for Extension of Time all replies		3	3	
	Terminal Disclaimer Filed		2	2	
	Miscellaneous Incoming Letter		1	1	
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30597	no	2
			ca2282ac63e31a53ce121b91538aec6f4dbf1dc5		
Warnings:					
Information:					
Total Files Size (in bytes):			1772507		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: WILTON *et al.*

Applicant: The University of Western
Australia

Application No.: 15/705,172

Filed: September 14, 2017

Confirmation No.: 2879

Art Unit: 1674

Examiner: Chong, Kimberly

Atty. Docket: 4140.01500A9

Title: **ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND
METHODS OF USE THEREOF**

**Authorization to Treat a Reply as Incorporating an
Extension of Time Under 37 C.F.R. § 1.136(a)(3)**

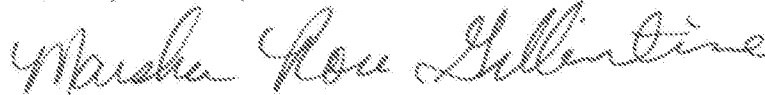
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Commissioner:

The U.S. Patent and Trademark Office is hereby authorized to treat any concurrent or future reply that requires a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. The U.S. Patent and Trademark Office is hereby authorized to charge all required extension of time fees to our Deposit Account No. 19-0036, if such fees are not otherwise provided for in such reply.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Marsha Rose Gillentine
Attorney for Applicant
Registration No. 58,403

Date: April 3, 2018

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600
9204639_1.docx

To: jcovert@sternekessler.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 153767

Apr 03, 2018 05:50:42 AM

Dear PAIR Customer:

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 153767 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

Disclaimer:

The list of documents shown below is provided as a courtesy and is not part of the official file wrapper. The content of the images shown in PAIR is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
15705172	N570	04/02/2018	4140.01500A9
	N570	04/02/2018	4140.01500A9

To view your correspondence online or update your email addresses, please visit us anytime at <https://portal.uspto.gov/secure/myportal/privatepair>.

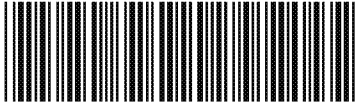
If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

37138

<i>Search Notes</i> 	Application/Control No. 15/705,172	Applicant(s)/Patent Under Reexamination WILTON et al.
	Examiner KIMBERLY CHONG	Art Unit 1674

CPC - Searched*		
Symbol	Date	Examiner
C07H 21/04	9/29/2017	KC

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
SEQ ID No. 195	9/29/2017	KC
PALM inventor name search	9/29/2017	KC
updated	03/21/2018	KC

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

Address: COMMISSIONER FOR PATENTS

P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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15/705,172

09/14/2017

Stephen Donald WILTON

4140.01500A9

2879

153767

7590

04/04/2018

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

1100 NEW YORK AVENUE, N.W.

WASHINGTON, DISTRICT OF COLUMBIA 20005

UNITED STATES OF AMERICA

EXAMINER

CHONG, KIMBERLY

ART UNIT

PAPER NUMBER

1674

MAIL DATE

DELIVERY MODE

04/04/2018

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Application No.

15/705,172

Applicant(s)

WILTON et al.

Office Action Summary

Examiner

KIMBERLY CHONG

Art Unit

1674

AIA Status

No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 01/05/2018.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a) ☒ This action is **FINAL**.

2b) ☐ This action is non-final.

3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☒ Claim(s) 2-3 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☒ Claim(s) 2-3 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10) ☐ The specification is objected to by the Examiner.

11) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some** c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

3) ☒ Interview Summary (PTO-413)

Paper No(s)/Mail Date 03/26/2018.

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)

4) ☐ Other: _____.

Paper No(s)/Mail Date 01/05/2018.

Application/Control Number: 15/705,172
Art Unit: 1674

Page 2

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Status of Application/Amendment/Claims

Claims 2 and 3 are pending and currently under examination.

Information Disclosure Statement

The submission of the Information Disclosure Statements on 01/05/2018 is in compliance with 37 CFR 1.97. The information disclosure statement has been considered by the examiner and signed copies have been placed in the file.

Response to Arguments

Claim Rejections - 35 USC § 103

The rejection of claims 2 and 3 under pre-AIA 35 U.S.C. 103(a) as being obvious over van Ommen (WO2004/083432 cited on IDS filed 09/22/2017) and Koenig et al. (Nature 338, 509 - 511 06 April 1989 cited on IDS filed 09/22/2017) is withdrawn in response to Applicant's argument that one of skill in the art would not have been motivated to make the claimed oligonucleotide from h53AON1 taught by van Ommen.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11

Application/Control Number: 15/705,172
Art Unit: 1674

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F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(I)(1) - 706.02(I)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/forms/. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to

<http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp>.

Application/Control Number: 15/705,172
Art Unit: 1674

Page 4

The rejection of claims 2 and 3 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 8,455,636 is withdrawn in response to Applicant's arguments.

The rejection of claims 2 and 3 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 8,232,384 is maintained for the reasons of record.

Patent '384 are drawn to an antisense oligonucleotide targeted to annealing site H53A (+23+47) and consisting of SEQ ID No. 195 which is 25 nucleotides in length. The instant claims are drawn to an antisense oligonucleotide targeted to annealing site H53A (+23+47) having 20-31 bases comprising at least 12 consecutive bases of SEQ ID No. 195 but could also encompass 25 nucleotides of SEQ ID No. 195. Therefore the instant claims and the claims of the patent are not patentably distinct from each other.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

Application/Control Number: 15/705,172
Art Unit: 1674

Page 5

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KIMBERLY CHONG **whose telephone number is** (571)272-3111. The examiner can normally be reached Monday thru Friday 9-5 pm.

If attempts to reach the examiner by telephone are unsuccessful please contact the SPE for 1674 Ram Shukla at 571-272-07350735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

Application/Control Number: 15/705,172
Art Unit: 1674

Page 6

For all other customer support, please call the USPTO Call Center (UCC) at 800-
786-9199.

/Kimberly Chong/
Primary Examiner
Art Unit 1674

37146

<i>Examiner-Initiated Interview Summary</i>	Application No. 15/705,172		Applicant(s) WILTON et al.	
	Examiner KIMBERLY CHONG		Art Unit 1674	AIA Status No

All participants (applicant, applicant's representative, PTO personnel):

(1) KIMBERLY CHONG. (3) ____.

(2) AMY MANDRAGOURAS. (4) ____.

Date of Interview: 27 March 2018.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: ____.

Issues Discussed ☐ 101 ☐ 112 ☐ 102 ☐ 103 ☐ Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: ____.

Identification of prior art discussed: ____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Called to tell Applicant's that the 103 rejection is withdrawn and to discuss double patenting rejection and whether Applicant's would file an eTerminal disclaimer since that is the only remaining rejection. I was informed this application has been transferred to a new law firm..

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/KIMBERLY CHONG/ Primary Examiner, Art Unit 1674	
---	--

Doc code: IDS

37147

PTO/SB/08a (03-15)

Doc description: Information Disclosure Statement (IDS) Filed

Approved for use through 07/31/2016. OMB 0651-0031

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		15705172
	Filing Date		2017-09-14
	First Named Inventor		Stephen Donald WILTON
	Art Unit		1674
	Examiner Name	K. Chong	
	Attorney Docket Number		AVN-008CN41

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	9758783		2017-09-12	Wilton et al.	

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Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20110046203	A1	2011-02-24	Wilton et al.	
	2	20170283799	A1	2017-10-05	KAYE	
	3	20170292125	A1	2017-10-12	SAZANI et al.	
	4	20170369875	A1	2017-12-28	BESTWICK et al.	
	5	20170369876	A1	2017-12-28	BESTWICK et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number # 37148	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	K. Chong
Attorney Docket Number	AVN-008CN41

6	20180002689	A1	2018-01-04	BESTWICK et al.
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If you wish to add additional U.S. Published Application citation information please click the Add button.

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FOREIGN PATENT DOCUMENTS

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Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ²	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T ⁵
	1							

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NON-PATENT LITERATURE DOCUMENTS

Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
	1	European Decision of the Opposition Division, European Application No. 10004274.6, dated December 19, 2017, 23 pages.	
	2	Extended European Search Report, EP 16172354.9, dated January 23, 2017, 7 pages.	
	3	Extended European Search Report, EP 17159328.8, dated September 5, 2017, 10 pages.	
	4	University of Western Australia v. Academisch Ziekenhuis Leiden, UWA Notice of Filing Priority Statement, 2 pages, Patent Interference No. 106,007, dated November 18, 2014 (Doc 215)	

If you wish to add additional non-patent literature document citation information please click the Add button

Add

EXAMINER SIGNATURE

Examiner Signature	/KIMBERLY CHONG/ (04/02/2018)	Date Considered	
--------------------	-------------------------------	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	K. Chong
Attorney Docket Number	AVN-008CN41

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

Application Number # 37150	15705172
Filing Date	2017-09-14
First Named Inventor	Stephen Donald WILTON
Art Unit	1674
Examiner Name	K. Chong
Attorney Docket Number	AVN-008CN41

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

- ☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.
- ☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Amy E. Mandragouras, Esq./	Date (YYYY-MM-DD)	2018-01-05
Name/Print	Amy E. Mandragouras, Esq.	Registration Number	36,207

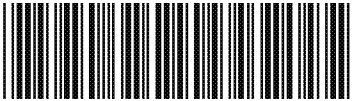
This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Application Number 	Application/Control No. 15/705,172	Applicant(s)/Patent under Reexamination WILTON ET AL.
Document Code - DISQ		Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	<input checked="" type="checkbox"/> APPROVED	<input type="checkbox"/> DISAPPROVED
Date Filed : 4/3/18	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
Felicia D. Roberts 8,232,384



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

153767 7590 04/26/2018
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DISTRICT OF COLUMBIA 20005
UNITED STATES OF AMERICA

EXAMINER

CHONG, KIMBERLY

ART UNIT

PAPER NUMBER

1674

DATE MAILED: 04/26/2018

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/705,172	09/14/2017	Stephen Donald WILTON	4140.01500A9	2879

TITLE OF INVENTION: ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$500	\$0.00	\$0.00	\$500	07/26/2018

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL
#: 37154

Complete and send this form, together with applicable fee(s), to: **Mail** **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

153767 7590 04/26/2018
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DISTRICT OF COLUMBIA 20005
UNITED STATES OF AMERICA

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/705,172	09/14/2017	Stephen Donald WILTON	4140.01500A9	2879

TITLE OF INVENTION: ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$500	\$0.00	\$0.00	\$500	07/26/2018

EXAMINER	ART UNIT	CLASS-SUBCLASS
CHONG, KIMBERLY	1674	536-024500

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

☐ Issue Fee

☐ Publication Fee (No small entity discount permitted)

☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)

☐ A check is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
 Address: COMMISSIONER FOR PATENTS
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 Alexandria, Virginia 22313-1450
 www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/705,172	09/14/2017	Stephen Donald WILTON	4140.01500A9	2879
153767	7590	04/26/2018	EXAMINER	
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.			CHONG, KIMBERLY	
1100 NEW YORK AVENUE, N.W.			ART UNIT	
WASHINGTON, DISTRICT OF COLUMBIA 20005			PAPER NUMBER	
UNITED STATES OF AMERICA			1674	

DATE MAILED: 04/26/2018

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
 (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b) (2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
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8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 15/705,172	Applicant(s) WILTON et al.	
	Examiner KIMBERLY CHONG	Art Unit 1674	AIA Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 04/04/2018.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are 2-3 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some *c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. <input type="checkbox"/> Notice of References Cited (PTO-892)	5. <input type="checkbox"/> Examiner's Amendment/Comment
2. <input type="checkbox"/> Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.	6. <input checked="" type="checkbox"/> Examiner's Statement of Reasons for Allowance
3. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.	7. <input type="checkbox"/> Other _____.
4. <input checked="" type="checkbox"/> Interview Summary (PTO-413), Paper No./Mail Date. <u>04/09/2018</u> .	

/KIMBERLY CHONG/ Primary Examiner, Art Unit 1674	
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Application/Control Number: 15/705,172
Art Unit: 1674

Page 2

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

The following is an examiner's statement of reasons for allowance: the Terminal Disclaimer filed 04/04/2018 is approved and overcomes the Double Patenting Rejection of claims 2 and 3.

Claims 2 and 3 are allowed.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **KIMBERLY CHONG** whose telephone number is (571)272-3111. The examiner can normally be reached Monday thru Friday between M-F 8:00am-4:30pm.

If attempts to reach the examiner by telephone are unsuccessful please contact the SPE for 1674 Ram Shukla at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now

Application/Control Number: 15/705,172
Art Unit: 1674

Page 3

contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Kimberly Chong/
Primary Examiner
Art Unit 1674

37160

<i>Applicant-Initiated Interview Summary</i>	Application No. 15/705,172		Applicant(s) WILTON et al.	
	Examiner KIMBERLY CHONG		Art Unit 1674	AIA Status No

All participants (applicant, applicants representative, PTO personnel):

(1) KIMBERLY CHONG. (3) ____.

(2) NEIL SHULL. (4) ____.

Date of Interview: 09 April 2018.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: ____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: ____.

Identification of prior art discussed: ____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Confirmed that the Terminal Disclaimer was filed and approved. Claims 2 and 3 are in condition for allowance.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/KIMBERLY CHONG/ Primary Examiner, Art Unit 1674	
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37161
Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record

A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
 Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.

All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

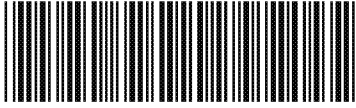
- 1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
- 2) an identification of the claims discussed,
- 3) an identification of the specific prior art discussed,
- 4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
- 5) a brief identification of the general thrust of the principal arguments presented to the examiner,
 (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
- 6) a general indication of any other pertinent matters discussed, and
- 7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

37162

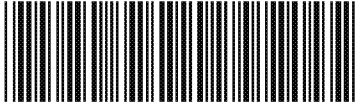
Issue Classification 	Application/Control No. 15/705,172	Applicant(s)/Patent Under Reexamination WILTON et al.
	Examiner KIMBERLY CHONG	Art Unit 1674

CPC						
Symbol					Type	Version
C12N	/	15	/	113	F	2013-01-01
C12N	/	2320	/	30	A	2013-01-01
C12N	/	2310	/	3341	A	2013-01-01
C12N	/	2310	/	321	A	2013-01-01
C12N	/	2310	/	315	A	2013-01-01
C12N	/	2310	/	3519	A	2013-01-01
C12N	/	2310	/	3233	A	2013-01-01
C12N	/	2310	/	11	A	2013-01-01
C12N	/	2320	/	33	A	2013-01-01
C12N	/	2310	/	33	A	2013-01-01

CPC Combination Sets					
Symbol			Type	Set	Ranking
	/				

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	2	
/KIMBERLY CHONG/ Primary Examiner, Art Unit 1674	14 April 2018	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

37163

Issue Classification 	Application/Control No. 15/705,172	Applicant(s)/Patent Under Reexamination WILTON et al.
	Examiner KIMBERLY CHONG	Art Unit 1674

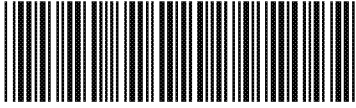
INTERNATIONAL CLASSIFICATION			
CLAIMED			
C07H	/	21	/ 04
NON-CLAIMED			
	/		/

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS
536	24.5

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	2	
/KIMBERLY CHONG/ Primary Examiner, Art Unit 1674	14 April 2018	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

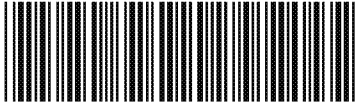
37164

Issue Classification 	Application/Control No. 15/705,172	Applicant(s)/Patent Under Reexamination WILTON et al.
	Examiner KIMBERLY CHONG	Art Unit 1674

<input checked="" type="checkbox"/> Claims renumbered in the same order as presented by applicant <input type="checkbox"/> CPA <input checked="" type="checkbox"/> T.D. <input type="checkbox"/> R.1.47															
CLAIMS															
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	2	
/KIMBERLY CHONG/ Primary Examiner, Art Unit 1674	14 April 2018	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

37165

Search Notes 	Application/Control No. 15/705,172	Applicant(s)/Patent Under Reexamination WILTON et al.
	Examiner KIMBERLY CHONG	Art Unit 1674

CPC - Searched*		
Symbol	Date	Examiner
C07H 21/04	9/29/2017	KC

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
SEQ ID No. 195	9/29/2017	KC
PALM inventor name search	9/29/2017	KC
updated	04/09/2018	KC

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
536	24.5	04/09/2018	KC

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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: **Mail** Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
 or **Fax** (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

153767 7590 04/26/2018
 STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
 1100 NEW YORK AVENUE, N.W.
 WASHINGTON, DISTRICT OF COLUMBIA 20005
 UNITED STATES OF AMERICA

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/705,172	09/14/2017	Stephen Donald WILTON	4140.01500A9	2879

TITLE OF INVENTION: ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$500	\$0.00	\$0.00	\$500	07/26/2018

EXAMINER	ART UNIT	CLASS-SUBCLASS
CHONG, KIMBERLY	1674	536-024500

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.

2. For printing on the patent front page, list
 (1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
 (2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
 2 Sterne, Kessler, Goldstein
 & Fox P.L.L.C.
 3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

The University of Western Australia

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Crawley, Australia

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

- ☒ Issue Fee
☐ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)

- ☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 19-0036 (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
☐ Applicant asserting small entity status. See 37 CFR 1.27
☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
 NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
 NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature

Typed or printed name

Eric K. Steffe

Date

Registration No.

36,688

Electronic Acknowledgement Receipt

EFS ID:	32457433
Application Number:	15705172
International Application Number:	
Confirmation Number:	2879
Title of Invention:	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF
First Named Inventor/Applicant Name:	Stephen Donald WILTON
Customer Number:	153767
Filer:	Neil P. Shull/Debbie Colonna
Filer Authorized By:	Neil P. Shull
Attorney Docket Number:	4140.01500A9
Receipt Date:	26-APR-2018
Filing Date:	14-SEP-2017
Time Stamp:	17:27:27
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	4140_01500A9_Filing_IssueFee.pdf	1007577 3747e1587b1b47d7367c0190dc44b5d5340e423e	no	1

Warnings:

Information:

Total Files Size (in bytes):

1007577

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

To: e-office@sternekessler.com,jcovert@sternekessler.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 153767

Apr 26, 2018 03:49:35 AM

Dear PAIR Customer:

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 153767 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

Disclaimer:

The list of documents shown below is provided as a courtesy and is not part of the official file wrapper. The content of the images shown in PAIR is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
15705172	NOA	04/26/2018	4140.01500A9
	INTV.SUM.APP	04/26/2018	4140.01500A9

To view your correspondence online or update your email addresses, please visit us anytime at <https://portal.uspto.gov/secure/myportal/privatepair>.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

APR-26-2018 18:54

SKGF

202 371 2540 P.001

ERIC K. STEFFE
DIRECTOR
(202) 772-8625
ESTEFFE@STERNEKESLER.COM

RECEIVED
CENTRAL FAX CENTER
APR 26 2018

Fax

☒ Urgent

☐ Return reply requested

☐ Original will be sent as confirmation

To: USPTO

Date: April 26, 2018

Attention: USPTO Fee Payment

Re: Appl. No. 15/705,172; Filed 09/14/17
For: ANTISENSE OLIGONUCLEOTIDES FOR
INDUCING EXON SKIPPING AND
METHODS OF USE THEREOF
Inventors: WILTON et al.

From: Debbie Colonna

Pages (including cover sheet): 2

Fax No: 571-273-8300

Our Reference: 4140.01500A9

Message

Submission of Issue Fee Payment (small entity) for Appl. No. 15/705,172

Certification of Facsimile Transmission

I hereby certify that this paper is being facsimile transmitted
to the Patent and Trademark Office on the date shown below.

Debbie Colonna
Name
Date: 4/26/2018

If any portion of this transmission is not received clearly or in full, contact us at the numbers below.

This message is intended for the exclusive use of the individual or entity to which it is addressed. The message may contain information that is privileged, confidential, or otherwise exempt from disclosure under applicable law. If the reader of this message is not the intended recipient, you are hereby notified that any dissemination, distribution, copying or use of this communication in any way is strictly prohibited. If you have received this communication in error, please call us collect immediately, and return the original message to us at the above address via the U.S. Postal Service.

PART B - FEE(S) TRANSMITTAL



Complete and send this form, together with applicable fee(s), to: **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
 or **Fax (571)-273-2885**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

153767 7590 04/26/2018
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DISTRICT OF COLUMBIA 20005
UNITED STATES OF AMERICA

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/705,172	09/14/2017	Stephen Donald WILTON	4140.01500A9	2879

TITLE OF INVENTION: ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

APPL. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$500	\$0.00	\$0.00	\$500	07/26/2018

EXAMINER	ART UNIT	CLASS-SUBCLASS
CHONG, KIMBERLY	1674	536-024500

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1. _____
2. Sterne, Kessler, Goldstein
& Fox P.L.L.C.
3. _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

The University of Western Australia

(B) RESIDENCE (CITY and STATE OR COUNTRY)

Crawley, Australia

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

☒ Issue Fee

☐ Publication Fee (No small entity discount permitted)

☐ Advance Order - # of Copies _____

4b. Payment of Fee(s); (Please first reapply any previously paid issue fee shown above)

☐ A check is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 19-0036 (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29.

☐ Applicant asserting small entity status. See 37 CFR 1.27.

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature Eric K. Steffe Date April 26, 2018

Typed or printed name Eric K. Steffe

Registration No. 04/26/2018 H050886 00000024 190036 15705172



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/705,172	09/14/2017	Stephen Donald WILTON	4140.01500A9	2879

7590 05/03/2018
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER

CHONG, KIMBERLY

ART UNIT	PAPER NUMBER
----------	--------------

1674

DATE MAILED: 05/03/2018

PRIORITY ACKNOWLEDGMENT

- ☐ 1. Receipt is acknowledged of priority papers submitted under 35 U.S.C. 119. The papers have been placed of record in the file.
- ☒ 2. Applicant's claim for priority, based on papers filed in parent Application Number 11/570,691 submitted under 35 U.S.C. 119, is acknowledged.
- ☐ 3. The priority papers, submitted _____, after payment of the issue fee are
- ☐ acknowledged
- While the priority claim or certified copy filed will be placed in the file record, neither will be reviewed and the patent when published will not include the priority claim.
- See 37 CFR 1.55(a)(2).
- ☐ not acknowledged since the processing fee in 37 CFR 1.17(i) has not been received.
- ☐ 4. For utility and plant applications filed on or after November 29, 2000, the priority claim is not entered because the claim was not presented within the time limit required by 37 CFR 1.55(a)(1). A petition to accept a delayed claim for priority under 35 U.S.C. 119(a) - (d) or (f), or 365(a) may be filed. See 37 CFR 1.55(c) and MPEP 201.14(a).

74/2, Por

571-272-4200 or 1-888-786-0101
Application Assistance Unit
Office of Data Management

To: e-office@sternekessler.com,jcovert@sternekessler.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 153767

May 05, 2018 07:36:42 AM

Dear PAIR Customer:

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 153767 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

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Application	Document	Mailroom Date	Attorney Docket No.
15705172	M327	05/03/2018	4140.01500A9

To view your correspondence online or update your email addresses, please visit us anytime at <https://sportal.uspto.gov/secure/myportal/privatepair>.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

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Thank you for prompt attention to this notice,

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Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/705,172	06/12/2018	9994851	4140.01500A9	2879

153767 7590 05/23/2018
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site <http://pair.uspto.gov> for additional applicants):

The University of Western Australia, Crawley, AUSTRALIA;
Stephen Donald WILTON, Applecross, AUSTRALIA;
Sue FLETCHER, Bayswater, AUSTRALIA;
Graham MCCLOREY, Bayswater, AUSTRALIA;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

To: e-office@sternekessler.com,jcovert@sternekessler.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 153767

May 24, 2018 04:04:25 AM

Dear PAIR Customer:

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 153767 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

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Application	Document	Mailroom Date	Attorney Docket No.
15705172	ISSUE.NTF	05/23/2018	4140.01500A9

To view your correspondence online or update your email addresses, please visit us anytime at <https://sportal.uspto.gov/secure/myportal/privatepair>.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: WILTON *et al.*

Confirmation No.: 2879

Applicant: The University of Western
Australia

Art Unit: 1674

Application No.: 15/705,172

Examiner: Chong, Kimberly

Filing Date: September 14, 2017

Atty. Docket: 4140.01500A9

Title: **ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND
METHODS OF USE THEREOF**

**Statement of Substance of Interview
In Accordance With 37 C.F.R. § 1.133(b) and M.P.E.P. § 713.04**

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

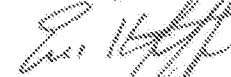
Commissioner:

In reply to the Interview Summary (Form PTOL-413) mailed by the U.S. Patent & Trademark Office with the Notice of Allowance on April 26, 2018, Applicant submits herewith the following Statement of Substance of the Interview held with Examiner Kimberly Chong, on April 9, 2018, regarding the above captioned application.

During the interview, the Examiner confirmed that the Terminal Disclaimer filed on April 3, 2018 was approved and that the application would be allowed.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Eric K. Steffe
Attorney for Applicant
Registration No. 36,688

Date: 5/29/18

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

9396506_1.docx

Electronic Acknowledgement Receipt

EFS ID:	32743284
Application Number:	15705172
International Application Number:	
Confirmation Number:	2879
Title of Invention:	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF
First Named Inventor/Applicant Name:	Stephen Donald WILTON
Customer Number:	153767
Filer:	Neil P. Shull/Debbie Colonna
Filer Authorized By:	Neil P. Shull
Attorney Docket Number:	4140.01500A9
Receipt Date:	29-MAY-2018
Filing Date:	14-SEP-2017
Time Stamp:	15:14:10
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant summary of interview with examiner	4140_01500A9_Filing_StatementSubstanceofInterview.pdf	407819 99efaf6ce36c6152beb4a1384d600e3f93a73e8b	no	1

Warnings:

Information:

Total Files Size (in bytes):

407819

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/47 (03-09)

Approved for use through 05/31/2015. OMB 0651-0016

U.S. Patent and Trademark Office; U. S. DEPARTMENT OF COMMERCE

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Fax to:
571-273-6500

- OR -

INSTRUCTIONS: The issue fee must have been paid for application(s) listed on this form. In addition, only an address represented by a Customer Number can be established as the fee address for maintenance fee purposes (hereafter, fee address). A fee address should be established when correspondence related to maintenance fees should be mailed to a different address than the correspondence address for the application. **When to check the first box below:** If you have a Customer Number to represent the fee address. **When to check the second box below:** If you have no Customer Number representing the desired fee address, in which case a completed Request for Customer Number (PTO/SB/125) must be attached to this form. For more information on Customer Numbers, see the Manual of Patent Examining Procedure (MPEP) § 403.

For the following listed application(s), please recognize as the "Fee Address" under the provisions of 37 CFR 1.363 the address associated with:

☒ Customer Number: 154896

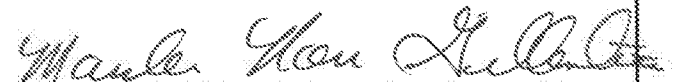
OR

☐ The attached Request for Customer Number (PTO/SB/125) form.

PATENT NUMBER (if known)	APPLICATION NUMBER
9,994,851	15/705,172

Completed by (check one):

☐ Applicant/Inventor


Signature

☒ Attorney or Agent of record 58,403
(Reg. No.)

Marsha Rose Gillentine
Typed or printed name

☐ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

(202) 371-2600
Requester's telephone number

☐ Assignee recorded at Reel _____ Frame _____

Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.363. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 5 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND COMPLETE D FORMS TO THIS ADDRESS. **SEND TO: Mail Stop M Correspondence, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

SRPT-VYDS-0004985

Electronic Acknowledgement Receipt

EFS ID:	33011664
Application Number:	15705172
International Application Number:	
Confirmation Number:	2879
Title of Invention:	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF
First Named Inventor/Applicant Name:	Stephen Donald WILTON
Customer Number:	153767
Filer:	Marsha Rose Gillentine
Filer Authorized By:	
Attorney Docket Number:	4140.01500A9
Receipt Date:	26-JUN-2018
Filing Date:	14-SEP-2017
Time Stamp:	18:24:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	4140_01500A9_Fee_Address_Indication_Form.pdf	165669 9804f1317f83faa445c0b93a6b2ad6474a1548c7	no	1

Warnings:

Information:**Total Files Size (in bytes):**

165669

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent No.: 9,994,851

Confirmation No.: 2879

Date of Patent: June 12, 2018

Art Unit: 1674

Inventors: WILTON *et al.*

Atty. Docket: 4140.01500A9

Title: **ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF**

**Request for Certificate of Correction
Under 37 C.F.R. § 1.323 For Applicant's Mistake**

Attn: Certificate of Correction Branch

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Commissioner:

It is hereby requested that a Certificate of Correction under 37 C.F.R. § 1.323 be issued for the above-captioned United States Patent. This Certificate of Correction is being requested due to mistakes which appear in the printed patent. The mistakes made by Inventors are of a clerical or typographical nature, or of a minor character. Patentees submit that correction of these errors does not introduce new matter.

Specifically, the printed patent contains the following errors for which a Certificate of Correction is respectfully requested:

In the specification

Column 1, Line 26, before "STATEMENT REGARDING SEQUENCE LISTING", insert:

--STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

This invention was made with government support under grant number R01 NS044146 awarded by the National Institutes of Health. The government has certain rights in the invention.--

- 2 -

WILTON *et al.*
U.S. Patent No. 9,994,851

Remarks

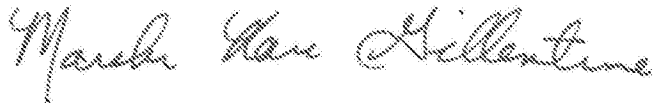
The above-noted corrections do not involve such changes in the patent as would constitute new matter or would require reexamination.

A completed Form PTO/SB/44 accompanies this request, with the above-noted corrections printed thereon. Accordingly, a Certificate of Correction is believed proper and issuance thereof is respectfully requested.

This request is accompanied by payment of the fee set forth in 37 C.F.R. § 1.20(a). Fee payment is provided through online credit card payment. The Commissioner is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Marsha Rose Gillentine
Attorney for Patentees
Registration No. 58,403

Date: June 29, 2018

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

9578306_1.docx

SRPT-VYDS-0004989

**UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION**

Page 1 of 1

PATENT NO. : 9,994,851

APPLICATION NO. : 15/705,172

ISSUE DATE : June 12, 2018

INVENTOR(S) : WILTON *et al.*

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the specification

Column 1, Line 26, before "STATEMENT REGARDING SEQUENCE LISTING", insert:

--STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

This invention was made with government support under grant number R01 NS044146 awarded by the National Institutes of Health. The government has certain rights in the invention.--

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue, NW
Washington DC 20005-3934

Atty. Dkt. No. 4140.01500A9

This collection of information is required by 37 CFR 1.322, 1.323 and 1.324. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1.0 hour to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you are required to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Attention Certificate of Corrections Branch, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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SRPT-VYDS-0004990

Electronic Patent Application Fee Transmittal				
Application Number:		15705172		
Filing Date:		14-Sep-2017		
Title of Invention:		ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF		
First Named Inventor/Applicant Name:		Stephen Donald WILTON		
Filer:		Marsha Rose Gillentine/Beverly Swann		
Attorney Docket Number:		4140.01500A9		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
CERTIFICATE OF CORRECTION	1811	1	150	150

37186

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				150

Electronic Acknowledgement Receipt

EFS ID:	33045562
Application Number:	15705172
International Application Number:	
Confirmation Number:	2879
Title of Invention:	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF
First Named Inventor/Applicant Name:	Stephen Donald WILTON
Customer Number:	153767
Filer:	Marsha Rose Gillentine/Beverly Swann
Filer Authorized By:	Marsha Rose Gillentine
Attorney Docket Number:	4140.01500A9
Receipt Date:	29-JUN-2018
Filing Date:	14-SEP-2017
Time Stamp:	13:04:06
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$ 150
RAM confirmation Number	062918INTEFSW13042600
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	414001500A9Ptocover.pdf	260801	no	1
			88ce2cc4e2806e54a54265eb2620088de49d84cf		
Warnings:					
Information:					
2	Request for Certificate of Correction	414001500A9Request.pdf	140390	no	2
			505e877b7f4400beaba290056a09b206840c736c		
Warnings:					
Information:					
3	Request for Certificate of Correction	414001500A9COC.pdf	132779	no	1
			727d3a3f4034370a2970357ac31ce04c303b1f65		
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30421	no	2
			b2b1564d3e79221ee3ea74964264093ce7492c7f		
Warnings:					
Information:					
Total Files Size (in bytes):			564391		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



MARSHA ROSE GILLENTINE
DIRECTOR
(202) 772-8692
MGILLENTINE@STERNEKESSLER.COM

June 29, 2018

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Confirmation No. 2879
Art Unit 1674

Re: U.S. Patent No. 9,994,851; Issue Date: June 12, 2018
(from U.S. Appl. No. 15/705,172; Filing Date: September 14, 2017)
For: **ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON
SKIPPING AND METHODS OF USE THEREOF**
Inventors: WILTON *et al.*
Our Ref: 4140.01500A9

Commissioner:

Transmitted herewith for appropriate action are the following documents:

1. Online Credit Card Payment Authorization in the amount of \$150.00 to cover fee for Request for Certificate of Correction;
2. Request for Certificate of Correction Under 37 C.F.R. § 1.323 For Applicant's Mistake; and
3. Certificate of Correction (PTO/SB/44).

The above-listed documents are filed electronically.

Fee payment is provided through online credit card payment. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency or credit any overpayment to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Marsha Rose Gillentine
Attorney for Patentees
Registration No. 58,403

MRG/ABM/mwf
Enclosures

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 9,994,851 B2
APPLICATION NO. : 15/705172
DATED : June 12, 2018
INVENTOR(S) : Wilton et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:


In the Specification

Column 1, Line 26, before "STATEMENT REGARDING SEQUENCE LISTING", insert:

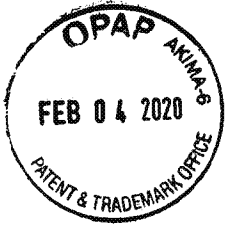
--STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

This invention was made with government support under grant number R01 NS044146 awarded by the National Institutes of Health. The government has certain rights in the invention.--

Signed and Sealed this
Thirty-first Day of July, 2018



Andrei Iancu
Director of the United States Patent and Trademark Office



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 9,994,851 B2

Issued: June 12, 2018

Assignee: The University of Western
Australia

Atty. Docket: 4140.01500A9/EKS/MRG/THN

For: **Antisense Oligonucleotides for
Inducing Exon Skipping and
Methods of Use Thereof**

Mail Stop Hatch-Waxman PTE
Office of Patent Legal Administration
Room MDW 7B 85
600 Dulany Street (Madison Building)
Alexandria, VA 22314

FEE TRANSMITTAL LETTER
FOR AN APPLICATION FOR EXTENSION UNDER 35 U.S.C. § 156

Commissioner:

Transmitted herewith is an Application for Extension of Patent Term Under 35 U.S.C. § 156 for U.S. Patent No. 9,994,851 B2, accompanied by two additional copies. The undersigned attorney for Applicant hereby states that these copies are certified to be duplicates of the original. Each copy contains the following attachments:

Attachment A	Executed Power of Attorney and Notice of Acceptance of Power of Attorney
Attachment B	Agency Letter authorizing The University of Western Australia to rely upon the activities of Sarepta
Attachment C	Package insert describing the Approved Product VYONDYS 53™
Attachment D	FDA Approval Letter for VYONDYS 53™
Attachment E	U.S. Patent No. 9,994,851 B2
Attachment F	Terminal Disclaimer filed in U.S. Application No. 15/705,172, now U.S. Patent No. 9,994,851 B2
Attachment G	Certificate of Correction issued for U.S. Patent No. 9,994,851 B2
Attachment H	FDA Letter dated November 17, 2014, substantiating the IND submission date

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U.S. Patent No. 9,994,851 B2
Atty. Dkt. No. 4140.01500A9/EKS/MRG/THN

Attachment I	FDA Letter dated January 28, 2016, substantiating the date of authorization of clinical studies
Attachment J	FDA Letter dated January 3, 2019, substantiating the NDA number and the initial NDA submission date
Attachment K	Chronology of Events on VYONDYS 53™

Please find a Credit Card payment Form for the \$1,120.00 fee estimated to be due in connection with this Application. The Commissioner is hereby authorized to charge any additional fees, which may be required, or credit any overpayment to Sterne, Kessler, Goldstein & Fox P.L.L.C. Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

/Eric K. Steffe/

Eric K. Steffe
Attorney for Applicant
Registration No. 36,688

Date: 2/4/2020

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United States Patent and Trademark Office

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02/04/2020

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 9,994,851 B2

Issued: June 12, 2018

Assignee: The University of Western
Australia

Atty. Docket: 4140.01500A9/EKS/MRG/THN

For: **Antisense Oligonucleotides for
Inducing Exon Skipping and
Methods of Use Thereof**

Application for Extension of Patent Term Under 35 U.S.C. § 156

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Mail Stop Hatch-Waxman PTE

Commissioner:

Applicant, **The University of Western Australia**, represents that it is the assignee of the entire interest in and to Letters Patent of U.S. Patent No. 9,994,851 B2 granted to Stephen Donald Wilton, Sue Fletcher, and Graham McClorey on June 12, 2018, for **Antisense Oligonucleotides for Inducing Exon Skipping and Methods of Use Thereof** by virtue of an Assignment from the inventors to The University of Western Australia recorded September 25, 2017, Reel 043682, Frame 0261.

The undersigned Attorney for Applicant is authorized to act on behalf of The University of Western Australia. Copies of the executed Power of Attorney and Notice of Acceptance of Power of Attorney are enclosed as Attachment A.

Sarepta Therapeutics, Inc. ("Sarepta") and ST International Holdings Two, Inc. are the exclusive licensees of U.S. Patent No. 9,994,851 B2 by virtue of an Exclusive License Agreement effective as of November 24, 2008, and amended and restated as of April 10, 2013, and further by virtue of an Assignment and Assumption Agreement

effective as of August 31, 2018. Sarepta was the marketing applicant of the approved product, VYONDYS 53™ (golodirsen) injection (hereinafter referred to as VYONDYS 53™), before the Food and Drug Administration ("FDA"). Applicant submits that there has been an agency relationship between The University of Western Australia and Sarepta during the regulatory review period of VYONDYS 53™. To show that The University of Western Australia is authorized to rely upon activities of Sarepta before the FDA, a copy of a letter from Sarepta specifically authorizing The University of Western Australia to rely upon such activities and file this Application for Extension of Patent Term based on the regulatory review period of VYONDYS 53™ is attached as Attachment B.

Applicant hereby submits this application for extension of the patent term under 35 U.S.C. § 156 by providing the following information required by the rules promulgated by the U.S. Patent and Trademark Office (37 C.F.R. §§ 1.710-1.740 and 1.775). For the convenience of the Patent and Trademark Office, the information contained in this application is presented in a format which follows the requirements of Section 1.740 of Title 37 of the Code of Federal Regulations.

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.

The approved product, VYONDYS 53™, is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping. VYONDYS 53™ is a sterile, aqueous, preservative-free, concentrated solution for dilution prior to intravenous administration. VYONDYS 53™ is a clear to slightly opalescent, colorless liquid. VYONDYS 53™ is

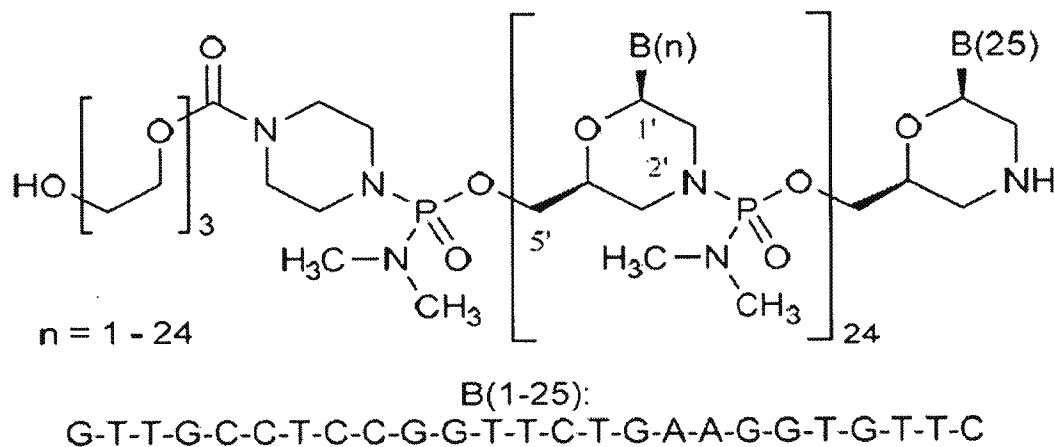
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supplied in single-dose vials containing 100 mg golodirsen (50 mg/ml). VYONDYS 53™ is formulated as an isotonic phosphate buffered saline solution with an osmolarity of 260 to 320 mOSM and a pH of 7.5. Each milliliter of VYONDYS 53™ contains: 50 mg golodirsen; 0.2 mg potassium chloride; 0.2 mg potassium phosphate monobasic; 8 mg sodium chloride; and 1.14 mg sodium phosphate dibasic, anhydrous, in water for injection. The product may contain hydrochloric acid or sodium hydroxide to adjust pH.

The active ingredient in VYONDYS 53™ is golodirsen, which is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass. The base sequence of golodirsen is 25 bases in length of the sequence from the 5' end to 3' end: GTTGCTCCGGTTCTGAAGGTGTTC. The molecular formula of golodirsen is C₃₀₅H₄₈₁N₁₃₈O₁₁₂P₂₅ and the molecular weight is 8647.28 daltons. The CAS Registry Number for golodirsen is 1422959-91-8.

The structure of golodirsen is as follows:



The chemical names of golodirsen include:

1. RNA, [*P*-deoxy-*P*-(dimethylamino)](2',3'-dideoxy-2',3'-imino-2',3'-seco)(2'a→5')(G-m⁵U-m⁵U-G-C-C-m⁵U-C-C-G-G-m⁵U-m⁵U-C-m⁵U-G-A-A-G-G-m⁵U-

G-m⁵U-m⁵U-C), 5'-[P-[4-[[2-[2-(2-hydroxyethoxy)ethoxy]ethoxy]carbonyl]-1-piperazinyl]-N,N-dimethylphosphonamidate]; and

2. all-*P*-ambo-[2',3'-azanediyl]-*P*-(dimethylamino)-*P*-2',3'-trideoxy-2',3'-seco] (2'-N→5')(G-T-T-G-C-C-T-C-C-G-G-T-T-C-T-G-A-A-G-C-T-G-T-T-C) 5'-{P-[4-({2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}carbonyl)piperazin-1-yl]-N,N-dimethylphosphonamidate}.

Golodirsén is designed to bind to exon 53 of human dystrophin pre-mRNA resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 53 skipping.

A copy of the package insert describing the approved product is attached as Attachment C.

(2) *A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.*

The approved product was subject to regulatory review under the Federal Food, Drug, and Cosmetic Act (FDCA), Section 505(b).

(3) *An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.*

The approved product received permission for commercial marketing or use under Section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) on **December 12, 2019**. A copy of the Approval Letter from the Food and Drug Administration is attached as Attachment D.

(4) *In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.*

The active ingredient in VYONDYS 53™ is golodirsen, which on information and belief, has not been previously approved for commercial marketing or use, either alone or in combination, under the Public Health Service Act, the Virus-Serum-Toxin Act, or under Section 505 of the Federal Food, Drug, and Cosmetic Act.

(5) *A statement that the application is being submitted within the sixty day period permitted for submission pursuant to §1.720(f) and an identification on the date of the last day on which the application could be submitted.*

The application for extension of patent term under 35 U.S.C. § 156 is being submitted within the permitted 60-day period pursuant to 37 C.F.R. § 1.720(f). The last day on which this application could be submitted is **February 9, 2020** (a Sunday).

(6) *A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.*

The complete identification of the patent for which a term extension is being sought is as follows:

Inventors: Stephen Donald Wilton; Sue Fletcher; and Graham McClorey

Patent No.: US 9,994,851 B2¹

Issue Date: June 12, 2018

Expiration Date: June 28, 2025 (*i.e.*, 20 years from its earliest effective date of June 28, 2005)

(7) *A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.*

A copy of U.S. Patent No. 9,994,851 B2, the patent for which an extension is being sought is attached (Attachment E).

(8) *A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.*

¹ US 9,994,851 B2 issued from application No. 15/705,172 ("the '172 application"), filed on September 14, 2017. The '172 application is a continuation of application No. 15/274,772 ("the '772 application"), filed on September 23, 2016. The '772 application is a continuation of application No. 14/740,097 ("the '097 application"), filed on June 15, 2015, now U.S. Patent No. 9,605,262. The '097 application is a continuation of application No. 13/741,150, filed on January 14, 2013, which is a continuation of application No. 13/168,857 ("the '857 application"), filed on June 24, 2011, now abandoned. The '857 application is a continuation of application No. 12/837,359 ("the '359 application"), filed on July 15, 2010, now U.S. Patent No. 8,232,384. The '359 application is a continuation of application No. 11/570,691, filed as application No. PCT/AU2005/000943 on June 28, 2005, now U.S. Patent No. 7,807,816.

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Atty. Dkt. No. 4140.01500A9/EKS/MRG/THN

A Terminal Disclaimer has been issued on this patent. Enclosed is a copy of the Terminal Disclaimer filed on April 3, 2018 (Attachment F), and approved on April 4, 2018. No Reexamination Certificate has been issued on this patent. A Certificate of Correction has been issued on this patent a copy of which is enclosed (Attachment G). No maintenance fee has been paid yet for this patent. The window for the first maintenance fee will open on June 12, 2021.

(9) *A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one claim reads on: (i) The approved product, if the listed claims include any claim to the approved product; (ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and (iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product.*

Claims 1 and 2 of U.S. Patent No. 9,944,851 B2 read on the approved product (see Table 1 below).

Table 1²

Claims of 9,994,851 B2	Claim reads on VYONDYS 53TM
Claim 1. An antisense oligonucleotide of 20 to 31 bases comprising	The active pharmaceutical ingredient in VYONDYS 53 TM is golodirsén which is an antisense oligonucleotide of 25 bases.
a base sequence that is 100% complementary to consecutive bases of a target region of exon 53	The sequence of bases from the 5' end to 3' end of golodirsén is GTTGCCTCCGGTTCTGAAGGTGTTC designed to bind to exon 53 of human dystrophin pre-

² This table is provided to show that the claims read on VYONDYS 53TM. The table is not intended to express an opinion on the construction of any particular term.

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Atty. Dkt. No. 4140.01500A9/EKS/MRG/THN

of the human dystrophin pre-mRNA,	mRNA.
wherein the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69),	The target region for golodirsen is annealing site H53A(+36+60).
wherein the base sequence comprises at least 12 consecutive bases of <i>CUG AAG GUG UUC UUG UAC UUC AUC C</i> (SEQ ID NO: 195), in which uracil bases are thymine bases, (emphasis added)	The sequence of bases from the 5' end to 3' end of golodirsen is G TTG CCT CCG GTT <i>CTG AAG GTG TTC</i> .
wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide,	Golodirsen is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass.
and wherein the antisense oligonucleotide induces exon 53 skipping;	Golodirsen is designed to bind to exon 53 of human dystrophin pre-mRNA resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 53 skipping.
or a pharmaceutically acceptable salt thereof.	
Claim 2. A pharmaceutical composition comprising:	VYONDYS 53™ is a colorless liquid available as injectable solution.
(i) an antisense oligonucleotide of 20 to 31 bases comprising	The active pharmaceutical ingredient in VYONDYS 53™ is golodirsen which is an antisense oligonucleotide of 25 bases.
a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA,	The sequence of bases from the 5' end to 3' end of golodirsen is GTTGCCTCCGGTTCTGAAGGTGTTC designed to bind to exon 53 of human dystrophin pre-mRNA.
wherein the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69),	The target region for golodirsen is annealing site H53A(+36+60).
wherein the base sequence comprises at least 12 consecutive bases of <i>CUG AAG GUG UUC UUG UAC UUC AUC C</i> (SEQ ID NO: 195), in which uracil bases are thymine bases, (emphasis	The sequence of bases from the 5' end to 3' end of golodirsen is G TTG CCT CCG GTT <i>CTG AAG GTG TTC</i> .

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Atty. Dkt. No. 4140.01500A9/EKS/MRG/THN

added)	
wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and	Golodirsen is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass.
wherein the antisense oligonucleotide induces exon 53 skipping,	Golodirsen is designed to bind to exon 53 of human dystrophin pre-mRNA resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 53 skipping.
or a pharmaceutically acceptable salt thereof; and	
(ii) a pharmaceutically acceptable carrier.	VYONDYS 53™ is formulated as an isotonic phosphate buffered saline solution.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

Pursuant to 37 C.F.R. 1.740(a)(10)(i), the relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(A) Investigational New Drug Application (IND 119982) for VYONDYS 53[™] was initially submitted on **November 7, 2014** and was received by the Food and Drug Administration on **November 7, 2014**, as confirmed by the letter from the FDA dated November 17, 2014. The FDA mailed a letter dated July 24, 2015, indicating that IND 119982 was under a full clinical hold. The FDA mailed a letter dated **January 28, 2016**, indicating that the clinical trials may be resumed. As such, IND 119982 became effective on **January 28, 2016**. A copy of the letter dated November 17, 2014 from the FDA substantiating the date of submission of IND, and a copy of the letter dated January 28, 2016 from the FDA substantiating the date of authorization of clinical studies are attached as Attachments H and I.

(B) New Drug Application (NDA) for VYONDYS 53[™] was submitted to the FDA on a rolling basis, and the submission of the NDA was completed on **December 19, 2018** (initial submission date). The NDA number assigned was 211970. A copy of the letter dated January 3, 2019, from the FDA substantiating

the NDA number and the initial submission date of **December 19, 2018**, is attached as Attachment J.

(C) On August 19, 2019, the FDA mailed a complete response letter indicating that the FDA cannot approve NDA 211970 in its present form. A complete response to the August 19, 2019, letter was submitted on November 27, 2019. The FDA approved NDA 211970 for VYONDYS 53[™] on **December 12, 2019**. A copy of the Approval Letter from the Food and Drug Administration is attached as Attachment D.

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(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

A brief description of significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to VYONDYS 53TM and the dates applicable to these significant activities are set forth in a chronology of events in Attachment K.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension period and a statement as to the length of extension claimed, including how the length of extension was determined.

(i) Applicant is of the opinion that U.S. Patent No. 9,994,851 B2 is eligible for extension of the patent term under 35 U.S.C. § 156 because it satisfies all requirements for such extension as follows:

(a) 35 U.S.C. § 156(a): *The term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended in accordance with this section from the original expiration date of the patent, which shall include any patent term adjustment granted under section 154(b) if—;*

U.S. Patent No. 9,994,851 B2 claims the product VYONDYS 53™.

(b) 35 U.S.C. § 156(a)(1): *the term of the patent has not expired before the application is submitted under subsection (d)(1) for its extension;*

U.S. Patent No. 9,994,851 B2 has not expired before submission of this application.

(c) 35 U.S.C. § 156(a)(2): *the term of the patent has never been extended under subsection (e)(1) of this section;*

The term of U.S. Patent No. 9,994,851 B2 has never been extended under 35 U.S.C. § 156(e)(1).

(d) 35 U.S.C. § 156(a)(3): *an application for extension is submitted by the owner of record of the patent or its agent and in accordance with the requirements of paragraphs (1) through (4) of subsection (d);*

The application for extension is submitted by the undersigned Attorney for Applicant, the owner of record, in accordance with the requirements of paragraphs (1) through (4) of 35 U.S.C. § 156(d) and the rules of the Patent and Trademark Office.

(e) 35 U.S.C. § 156(a)(4): *the product has been subject to a regulatory review period before its commercial marketing and use;*

VYONDYS 53™ has been subject to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. § 156(a)(5)(A): *except as provided in subparagraphs (B) or (C), the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred;*

The commercial marketing or use of VYONDYS 53™ after the regulatory review period is the first permitted commercial marketing or use under the provision of the Federal Food, Drug, and Cosmetic Act (i.e., Section 505) under which such regulatory review period occurred.

(g) 35 U.S.C. § 156(c)(4): *in no event shall more than one patent be extended under subsection (e)(1) for the same regulatory review period for any product.*

No other patent has been extended for the same regulatory review period for VYONDYS 53™.

(ii) The length of the extension of the patent term of U.S. Patent No. 9,994,851 B2 requested by Applicant is that period authorized by 35 U.S.C. § 156(c) which has been calculated to be 454 days. The length of the extension was calculated pursuant to 37 C.F.R. § 1.775 as follows:

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Atty. Dkt. No. 4140.01500A9/EKS/MRG/THN

(a) The regulatory review period under 35 U.S.C. § 156(g)(1)(B) began on **January 28, 2016** and ended **December 12, 2019**, which is a total of **1416** days, which is the sum of (1) and (2) below:

(1) The period of review under 35 U.S.C. § 156(g)(1)(B)(i), the "Testing Period," began on **January 28, 2016** and ended on **December 19, 2018**, which is **1057** days; and

(2) The period of review under 35 U.S.C. § 156 (g)(1)(B)(ii), the "Approval Period," began on **December 19, 2018**, and ended on **December 12, 2019**, which is a total of **359** days.

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph 12(ii)(a) above (**1416** days) less:

(1) The number of days in the regulatory review period which were on or before the date on which the patent issued (June 12, 2018), which is **867** days;

(2) The number of days during which applicant did not act with due diligence, which is zero (0) days; and

(3) One-half the number of days determined in sub-paragraph (12)(ii)(a)(1) above after the patent issued (one-half of 1057-867 days), which is **95** days.

(c) The number of days as determined in sub-paragraph (12)(ii)(b) ($1416 - 867 - 95 = 454$ days) when added to the expiration date of the original term of the patent (June 28, 2025) would result in the date of **September 25, 2026**.

(d) Fourteen (14) years when added to the date of approval of the NDA (December 12, 2019) would result in the date of **December 12, 2033**.

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(e) The earlier date as determined in sub-paragraphs (12)(ii)(c) and (12)(ii)(d) is **September 25, 2026**.

(f) Since U.S. Patent No. 9,994,851 B2 issued after September 24, 1984, the period of extension may not exceed five (5) years from the original expiration date of June 28, 2025. Five years when added to the original expiration date of the patent would result in the date of **June 28, 2030**.

(g) The earlier date as determined by sub-paragraph (12)(ii)(e) and (12)(ii)(f) is **September 25, 2026**.

(13) A statement that applicant acknowledges the duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought (see §1.765).

Applicant acknowledges the duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

In accordance with the duty of disclosure described in 37 C.F.R. §§ 1.740 and 1.765, Applicant informs the Commissioner that six patent term extension applications have been filed concurrently with respect to the regulatory review period for VYONDYS 53™. These patent term extension applications are with respect to U.S. Patent Nos. 9,994,851 B2 (the present application), RE47,691 E, 9,024,007 B2, 10,227,590 B2, 10,266,827 B2, and 10,421,966 B2. It is requested that the Office examine these patent term extension applications concurrently so that Applicant can elect, upon receipt of a

Notice of Final Determination and Requirement of Election, which patent to ultimately extend in accordance with 37 C.F.R. § 1.785.

(14) The prescribed fee for receiving and acting upon the application for extension (see §1.20(j)).

The prescribed fee for receiving and acting upon this application is attached in the amount of \$1,120.00. The Commissioner is authorized to charge any additional fees required by this application to Deposit Account No. 19-0036.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.

All correspondence and inquiries may be directed to the undersigned, whose address, telephone number and fax number are as follows:

Eric K. Steffe
Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue, N.W.
Washington, D.C. 20005
Phone: (202) 371-2600
Fax: (202) 371-2540

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Pursuant to 37 C.F.R. 1.740(b), the application for extension of patent term under 35 U.S.C. § 156 including its attachments and supporting papers is being submitted as one original and two (2) copies thereof.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

/Eric K. Steffe/

Eric K. Steffe
Attorney for Applicant
Registration No. 36,688

Date: 2/4/2020

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

Enclosures: Attachments A, B, C, D, E, F, G, H, I, J, and K
14490204v1

ATTACHMENT A



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/705,172	09/14/2017	Stephen Donald WILTON	4140.01500A9

CONFIRMATION NO. 2879

POA ACCEPTANCE LETTER

153767

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WASHINGTON, DC 20005



OC000000098475974

Date Mailed: 04/02/2018

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 03/28/2018.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at (571) 272-4000 or (571) 272-4200 or 1-888-786-0101.

/nbekele/

Doc Code: PA..

Document Description: Power of Attorney

PTO/AIA/82A (07-13)

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NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA/82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	15/705,172
Filing Date	September 14, 2017
First Named Inventor	Stephen Donald WILTON
Title	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF
Art Unit	1674
Examiner Name	CHONG, Kimberly
Attorney Docket Number	4140.01500A9

SIGNATURE of Applicant or Patent Practitioner

Signature	<i>Marsha Rose Gillentine</i>	Date (Optional)	<i>March 28, 2018</i>
Name	Marsha Rose Gillentine	Registration Number	58,403
Title (if Applicant is a juristic entity)			

Applicant Name (if Applicant is a juristic entity)

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☐

*Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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SRPT-VYDS-0005021

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Document Description: Power of Attorney

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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date
15/705,172	September 14, 2017

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

- ☒ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: **153767**
- OR
- ☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

- ☒ The address associated with the above-mentioned Customer Number
- OR
- ☐ The address associated with Customer Number: **153767**
- OR

Firm or Individual Name			
Address			
City	State	Zip	
Country			
Telephone	Email		

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

THE UNIVERSITY OF WESTERN AUSTRALIA

- ☐ Inventor or Joint Inventor (title not required below)
- ☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)
- ☒ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)
- ☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	<i>Robyn Owens</i>	Date (Optional)	
Name	Professor Robyn Owens		
Title	Deputy Vice-Chancellor (Research)		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☒ Total of **1** forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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ATTACHMENT B



SAREPTA

January 31, 2020

Via Email, Confirmation Via First Class Mail

The University of Western Australia
35 Stirling Highway
Crawley, WA 6009
Australia

Attn: Director, Office of Industry and Innovation

Re: U.S. Patent No. RE47,691 E, Issued: November 5, 2019
U.S. Patent No. 9,024,007 B2, Issued: May 5, 2015
U.S. Patent No. 9,994,851 B2, Issued: June 12, 2018
U.S. Patent No. 10,227,590 B2, Issued: March 12, 2019
U.S. Patent No. 10,266,827 B2, Issued: April 23, 2019
U.S. Patent No. 10,421,966 B2, Issued: September 24, 2019
Inventor(s): Stephen Donald Wilton *et al.*
Assignee: The University of Western Australia
Titled: **Antisense Oligonucleotides for Inducing Exon Skipping and Methods
of Use Thereof**

Dear Sir:

As you know, Sarepta Therapeutics, Inc. ("Sarepta") received approval of its NDA for VYONDYS 53™ (golodirsen) on December 12, 2019, from the U.S. Department of Health and Human Services, Food and Drug Administration ("FDA"). In addition, The University of Western Australia ("UWA") will timely file an Application for Patent Term Extension Under 35 U.S.C. § 156 in the United States Patent and Trademark Office in connection with the above-identified patents.

This letter serves to acknowledge the "agency relationship" (as defined in section 2752 of the Manual of Patent Examining Procedure) between UWA as the owner of the above-identified patents and Sarepta as the marketing applicant before the FDA during the regulatory review period. This letter further specifically authorizes UWA as the applicant for Patent Term Extension to rely on the activities of Sarepta as the marketing applicant before the FDA.

If you have any questions, please do not hesitate to contact one of us.

Very Truly Yours,

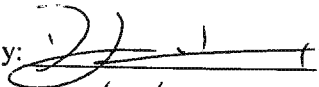
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SAREPTA

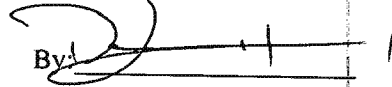
Sarepta Therapeutics, Inc.

ST International Holdings Two, Inc.

By: 

Date: 1/31/2020

Name: David Tyronne Howton, Jr.
Title: Executive Vice President,
General Counsel and Corporate Secretary

By: 

Date: 1/31/2020

Name: David Tyronne Howton, Jr.
Title: Manager

[Sarepta Letter of Authorization to UWA]

ATTACHMENT C

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VYONDYS 53™ safely and effectively. See full prescribing information for VYONDYS 53.

VYONDYS 53 (golodirsen) injection, for intravenous use
Initial U.S. Approval: 2019

INDICATIONS AND USAGE

VYONDYS 53 is an antisense oligonucleotide indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with VYONDYS 53. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials. (1)

DOSAGE AND ADMINISTRATION

- Measure glomerular filtration rate prior to initiation (2.1)
- 30 milligrams per kilogram once weekly (2.2)
- Administer as an intravenous infusion over 35 to 60 minutes (2.2, 2.4)
- Dilution required prior to administration (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/2 mL (50 mg/mL) in a single-dose vial (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- **Hypersensitivity Reactions:** Hypersensitivity reactions, including rash, pyrexia, pruritus, urticaria, dermatitis, and skin exfoliation have occurred in patients who were treated with VYONDYS 53. If a hypersensitivity reaction occurs, institute appropriate medical treatment and consider slowing the infusion or interrupting the VYONDYS 53 therapy. (2.3, 5.1)
- **Renal Toxicity:** Based on animal data, may cause renal toxicity. Renal function should be monitored; creatinine may not be a reliable measure of renal function in DMD patients. (5.2, 13.2)

ADVERSE REACTIONS

The most common adverse reactions (incidence $\geq 20\%$ and higher than placebo) were headache, pyrexia, fall, abdominal pain, nasopharyngitis, cough, vomiting, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sarepta Therapeutics, Inc. at 1-888-SAREPTA (1-888-727-3782) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2019

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VYONDYS 53 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with VYONDYS 53 [see *Clinical Studies (14)*]. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Monitoring to Assess Safety

Measurement of glomerular filtration rate prior to initiation of VYONDYS 53 and monitoring for renal toxicity during treatment is recommended [see *Warnings and Precautions (5.2)*].

2.2 Dosing Information

The recommended dose of VYONDYS 53 is 30 milligrams per kilogram administered once weekly as a 35 to 60-minute intravenous infusion.

If a dose of VYONDYS 53 is missed, it may be administered as soon as possible after the scheduled dose.

2.3 Preparation Instructions

VYONDYS 53 is supplied in single-dose vials as a preservative-free concentrated solution that requires dilution prior to administration. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Use aseptic technique.

- a. Calculate the total dose of VYONDYS 53 to be administered based on the patient's weight and the recommended dose of 30 milligrams per kilogram. Determine the volume of VYONDYS 53 needed and the correct number of vials to supply the full calculated dose.
- b. Allow the vials to warm to room temperature. Mix the contents of each vial by gently inverting 2 or 3 times. Do not shake.
- c. Visually inspect each vial of VYONDYS 53. The solution is a clear to slightly opalescent, colorless liquid. Do not use if the solution in the vials is discolored or particulate matter is present.
- d. With a syringe fitted with a 21-gauge or smaller bore non-coring needle, withdraw the calculated volume of VYONDYS 53 from the appropriate number of vials.

- e. Dilute the withdrawn VYONDYS 53 in 0.9% Sodium Chloride Injection, USP, to make a total volume of 100 to 150 mL. Gently invert 2 to 3 times to mix. Do not shake. Visually inspect the diluted solution for particulates.
- f. VYONDYS 53 contains no preservatives and should be administered immediately after dilution. Complete infusion of diluted VYONDYS 53 within 4 hours of dilution. If immediate use is not possible, the diluted product may be stored for up to 24 hours at 2°C to 8°C (36°F to 46°F). Do not freeze. Discard unused VYONDYS 53.

2.4 Administration Instructions

Application of a topical anesthetic cream to the infusion site prior to administration of VYONDYS 53 may be considered.

VYONDYS 53 is administered via intravenous infusion. Flush the intravenous access line with 0.9% Sodium Chloride Injection, USP, prior to and after infusion.

Infuse the diluted VYONDYS 53 over 35 to 60 minutes. Do not mix other medications with VYONDYS 53 or infuse other medications concomitantly via the same intravenous access line with VYONDYS 53.

If a hypersensitivity reaction occurs, consider slowing the infusion or interrupting the VYONDYS 53 therapy [see *Warnings and Precautions (5.1) and Adverse Reactions (6.1)*].

3 DOSAGE FORMS AND STRENGTHS

VYONDYS 53 is a clear to slightly opalescent, colorless liquid available as:

- Injection: 100 mg/2 mL (50 mg/mL) solution in a single-dose vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including rash, pyrexia, pruritus, urticaria, dermatitis, and skin exfoliation have occurred in VYONDYS 53-treated patients, some requiring treatment. If a hypersensitivity reaction occurs, institute appropriate medical treatment and consider slowing the infusion or interrupting the VYONDYS 53 therapy [see *Dosage and Administration (2.4)*].

5.2 Renal Toxicity

Renal toxicity was observed in animals who received golodirsén [see *Use in Specific Populations (8.4)*]. Although renal toxicity was not observed in the clinical studies with VYONDYS 53, renal toxicity, including potentially fatal glomerulonephritis, has been observed

after administration of some antisense oligonucleotides. Renal function should be monitored in patients taking VYONDYS 53. Because of the effect of reduced skeletal muscle mass on creatinine measurements, creatinine may not be a reliable measure of renal function in DMD patients. Measurement of glomerular filtration rate (GFR) by 24-hour urine collection prior to initiation of therapy is recommended. Monthly monitoring for proteinuria by dipstick urinalysis and monitoring of serum cystatin C every three months is recommended. In the case of a confirmed dipstick proteinuria of 2+ or greater or elevated serum cystatin C, a 24-hour urine collection to quantify proteinuria and assess GFR should be performed.

6 ADVERSE REACTIONS

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the VYONDYS 53 clinical development program, 58 patients received at least one intravenous dose of VYONDYS 53, ranging between 4 mg/kg (0.13 times the recommended dosage) and 30 mg/kg (the recommended dosage). All patients were male and had genetically confirmed Duchenne muscular dystrophy. Age at study entry was 6 to 13 years. Most (86%) patients were Caucasian.

VYONDYS 53 was studied in 2 double-blind, placebo-controlled studies.

In Study 1 Part 1, patients were randomized to receive once-weekly intravenous infusions of VYONDYS 53 (n=8) in four increasing dose levels from 4 mg/kg to 30 mg/kg or placebo (n=4), for at least 2 weeks at each level. All patients who participated in Study 1 Part 1 (n=12) were continued into Study 1 Part 2, an open-label extension, during which they received VYONDYS 53 at a dose of 30 mg/kg IV once weekly *[see Clinical Studies (14)]*.

In Study 2, patients received VYONDYS 53 (n=33) 30 mg/kg or placebo (n=17) IV once weekly for up to 96 weeks, after which all patients received VYONDYS 53 at a dose of 30 mg/kg.

Adverse reactions observed in at least 20% of treated patients in the placebo-controlled sections of Studies 1 and 2 are shown in Table 1.

Table 1: Adverse Reactions That Occurred in At Least 20% of VYONDYS 53-Treated Patients and at a Rate Greater than Placebo in Studies 1 and 2

Adverse Reaction	VYONDYS 53 (N = 41) %	Placebo (N = 21) %
Headache	41	10
Pyrexia	41	14
Fall	29	19
Abdominal pain	27	10
Nasopharyngitis	27	14
Cough	27	19
Vomiting	27	19
Nausea	20	10

Other adverse reactions that occurred at a frequency greater than 5% of VYONDYS 53-treated patients and at a greater frequency than placebo were: administration site pain, back pain, pain, diarrhea, dizziness, ligament sprain, contusion, influenza, oropharyngeal pain, rhinitis, skin abrasion, ear infection, seasonal allergy, tachycardia, catheter site related reaction, constipation, and fracture.

Hypersensitivity reactions have occurred in patients treated with VYONDYS 53 [see *Warnings and Precautions (5.1)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no human or animal data available to assess the use of VYONDYS 53 during pregnancy. In the U.S. general population, major birth defects occur in 2 to 4% and miscarriage occurs in 15 to 20% of clinically recognized pregnancies.

8.2 Lactation

Risk Summary

There are no human or animal data to assess the effect of VYONDYS 53 on milk production, the presence of golodirsén in milk, or the effects of VYONDYS 53 on the breastfed infant.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VYONDYS 53 and any potential adverse effects on the breastfed infant from VYONDYS 53 or from the underlying maternal condition.

8.4 Pediatric Use

VYONDYS 53 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping, including pediatric patients [see *Clinical Studies* (14)].

Intravenous administration of golodirsén (0, 100, 300, or 900 mg/kg) to juvenile male rats once weekly for 10 weeks (postnatal days 14 to 77) did not result in postnatal developmental (e.g., neurobehavioral, immune function, or male reproductive) toxicity. However, at the highest dose tested (900 mg/kg/week), golodirsén resulted in the death of animals because of renal impairment or failure. In surviving animals (including one animal at the lowest dose tested), there was a dose-dependent increase in the incidence and severity of renal tubular effects (including degeneration/regeneration, fibrosis, vacuolation, and dilatation), which correlated with changes in clinical pathology parameters, reflecting a dose-dependent impairment of renal function. In addition, decreases in bone area, mineral content, and mineral density were observed at the highest dose tested (900 mg/kg/week) but with no effect on bone growth. A no-effect dose for renal toxicity was not identified; the lowest dose tested (100 mg/kg/week) was associated with plasma exposures (AUC) approximately 2.5 times that in humans at the recommended human dose of 30 mg/kg/week.

8.5 Geriatric Use

DMD is largely a disease of children and young adults; therefore, there is no geriatric experience with VYONDYS 53.

8.6 Patients with Renal Impairment

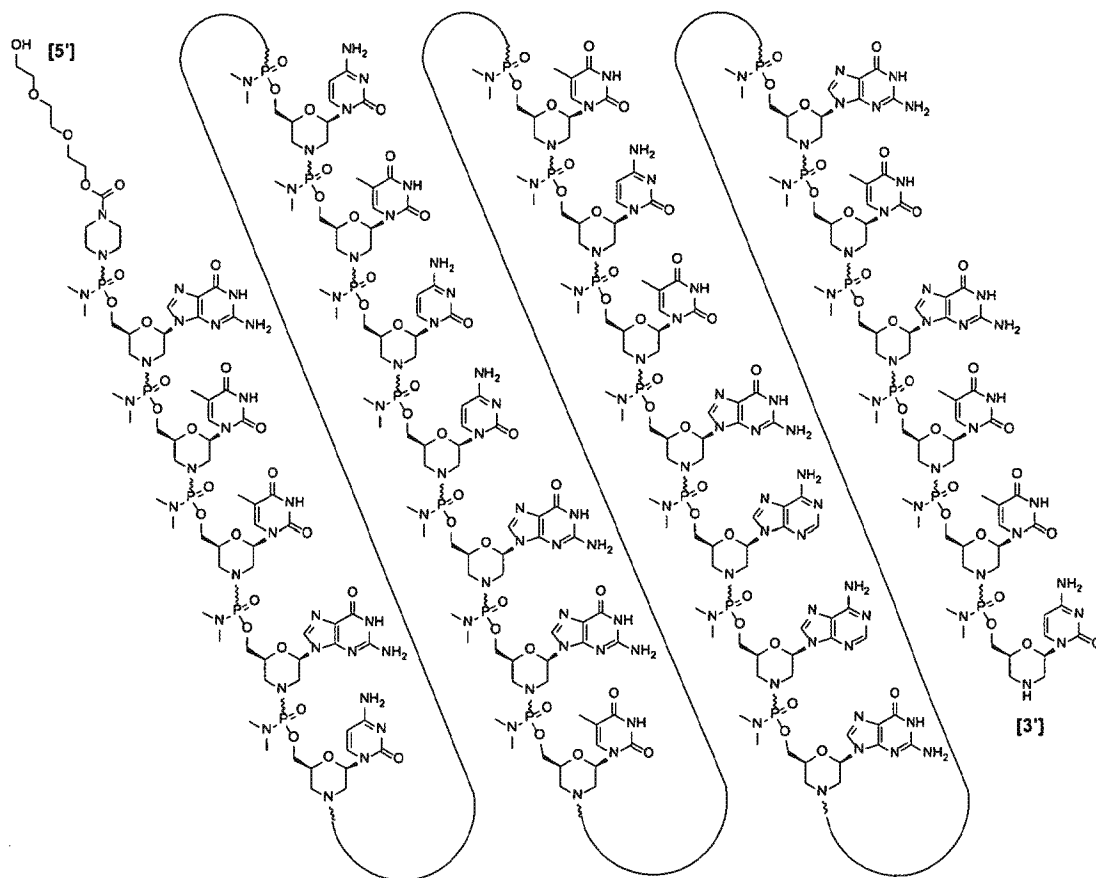
Renal clearance of golodirsén is reduced in non-DMD adults with renal impairment, based on estimated glomerular filtration rate calculated using the Modification of Diet and Renal Disease (MDRD) equation [see *Clinical Pharmacology* (12.3)]. However, because of the effect of reduced skeletal muscle mass on creatinine measurements in DMD patients, no specific dosage adjustment can be recommended for DMD patients with renal impairment based on estimated glomerular filtration rate. Patients with known renal function impairment should be closely monitored during treatment with VYONDYS 53.

11 DESCRIPTION

VYONDYS 53 (golodirsen) injection is a sterile, aqueous, preservative-free, concentrated solution for dilution prior to intravenous administration. VYONDYS 53 is a clear to slightly opalescent, colorless liquid. VYONDYS 53 is supplied in single-dose vials containing 100 mg golodirsen (50 mg/mL). VYONDYS 53 is formulated as an isotonic phosphate buffered saline solution with an osmolality of 260 to 320 mOSM and a pH of 7.5. Each milliliter of VYONDYS 53 contains: 50 mg golodirsen; 0.2 mg potassium chloride; 0.2 mg potassium phosphate monobasic; 8 mg sodium chloride; and 1.14 mg sodium phosphate dibasic, anhydrous, in water for injection. The product may contain hydrochloric acid or sodium hydroxide to adjust pH.

Golodirsen is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass. PMOs are synthetic molecules in which the five-membered ribofuranosyl rings found in natural DNA and RNA are replaced by a six-membered morpholino ring. Each morpholino ring is linked through an uncharged phosphorodiamidate moiety rather than the negatively charged phosphate linkage that is present in natural DNA and RNA. Each phosphorodiamidate morpholino subunit contains one of the heterocyclic bases found in DNA (adenine, cytosine, guanine, or thymine). Golodirsen contains 25 linked subunits. The sequence of bases from the 5' end to 3' end is GTTGCTCCGGTTCTGAAGGTGTTC. The molecular formula of golodirsen is $C_{305}H_{481}N_{138}O_{112}P_{25}$ and the molecular weight is 8647.28 daltons.

The structure of golodirsen is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Golodirsen is designed to bind to exon 53 of dystrophin pre-mRNA resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 53 skipping. Exon 53 skipping is intended to allow for production of an internally truncated dystrophin protein in patients with genetic mutations that are amenable to exon 53 skipping [see *Clinical Studies (14)*].

12.2 Pharmacodynamics

After treatment with VYONDYS 53, all patients evaluated (n=25) in Study 1 Part 2 [see *Clinical Studies (14)*] had an increase in skipping of exon 53 demonstrated by reverse transcription polymerase chain reaction (RT-PCR), compared to baseline.

In Study 1 Part 2 [see *Clinical Studies (14)*], dystrophin levels increased from 0.10% (SD 0.07) of normal at baseline to 1.02% (SD 1.03) of normal after 48 weeks of treatment with VYONDYS 53. The mean change from baseline in dystrophin after 48 weeks of treatment with VYONDYS

53 was 0.92% (SD 1.01) of normal levels ($p < 0.001$); the median change from baseline was 0.88%. This increase in dystrophin protein expression positively correlated with the level of exon skipping. Correct localization of truncated dystrophin to the sarcolemma in muscle fibers of patients treated with golodirsen was demonstrated by immunofluorescence staining.

12.3 Pharmacokinetics

The pharmacokinetics of golodirsen was evaluated in DMD patients following administration of intravenous doses ranging from 4 mg/kg/week to 30 mg/kg/week (i.e., recommended dosage). Golodirsen exposure increased proportionally with dose, with minimal accumulation with once-weekly dosing. Inter-subject variability (as %CV) for C_{max} and AUC ranged from 38% to 72%, and 34% to 44%, respectively.

Distribution

Steady-state volume of distribution was similar between DMD patients and healthy subjects. The mean golodirsen steady-state volume of distribution was 668 mL/kg (%CV=32.3) at a dose of 30 mg/kg. Golodirsen plasma protein binding ranged from 33% to 39% and is not concentration dependent.

Elimination

Golodirsen elimination half-life (SD) was 3.4 (0.6) hours, and plasma clearance was 346 mL/hr/kg at the 30 mg/kg dose.

Metabolism

Golodirsen is metabolically stable. No metabolites were detected in plasma or urine.

Excretion

Golodirsen is mostly excreted unchanged in the urine. The elimination half-life ($t_{1/2}$) was 3.4 hours.

Specific Populations

Age:

The pharmacokinetics of golodirsen have been evaluated in male pediatric DMD patients. There is no experience with the use of VYONDYS 53 in DMD patients 65 years of age or older.

Sex:

Sex effects have not been evaluated; VYONDYS 53 has not been studied in female patients.

Race:

The potential impact of race is not known because 92% of the patients in studies were Caucasians.

Patients with Renal Impairment:

The effect of renal impairment on the pharmacokinetics of golodirsen was evaluated in non-DMD subjects aged 41 to 65 years with Stage 2 chronic kidney disease (CKD) ($n=8$, estimated glomerular filtration rate (eGFR) ≥ 60 and < 90 mL/min/1.73 m²) or Stage 3 CKD ($n=8$, eGFR

≥ 30 and < 60 mL/min/1.73 m²) and matched healthy subjects (n=8, eGFR ≥ 90 mL/min/1.73 m²). Subjects received a single 30 mg/kg IV dose of golodirsen.

In subjects with Stage 2 or Stage 3 CKD, exposure (AUC) increased approximately 1.2-fold and 1.9-fold, respectively. There was no change in the C_{max} in subjects with Stage 2 CKD; in subjects with Stage 3 CKD, there was a 1.2-fold increase in C_{max} compared with subjects with normal renal function. The effect of Stage 4 or Stage 5 CKD on golodirsen pharmacokinetics and safety has not been studied.

Estimated GFR values derived from MDRD equations and the threshold definitions for various CKD stages in otherwise healthy adults would not be generalizable to pediatric patients with DMD. Therefore, no specific dosage adjustment can be recommended for patients with renal impairment [see *Use in Specific Populations* (8.6)].

Patients with Hepatic Impairment:

VYONDYS 53 has not been studied in patients with hepatic impairment.

Drug Interaction Studies

Golodirsen did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 *in vitro*. Golodirsen was a weak inducer of CYP1A2 and did not induce CYP2B6 or CYP3A4. Golodirsen was not metabolized by human hepatic microsomes and was not a substrate or strong inhibitor of any of the key human drug transporters tested (OAT1, OAT3, OCT2, OATP1B1, MATE1, P-gp, BCRP, and MRP2, OATP1B3 and MATE2-K). Based on *in vitro* data, golodirsen has a low potential for drug-drug interactions in humans.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies have not been conducted with golodirsen.

Mutagenesis

Golodirsen was negative in *in vitro* (bacterial reverse mutation and chromosomal aberration in CHO cells) and *in vivo* (mouse bone marrow micronucleus) assays.

Impairment of Fertility

Fertility studies in animals were not conducted with golodirsen. No effects of golodirsen on the male reproductive system were observed following weekly subcutaneous administration (0, 120, 300, or 600 mg/kg to male mice or weekly intravenous administration (0, 80, 200, or 400 mg/kg) to male monkeys. Plasma exposure (AUC) at the highest doses tested in mouse and monkey are approximately 10 and 45 times that in humans at the recommended weekly intravenous dose of 30 mg/kg.

13.2 Animal Toxicology and/or Pharmacology

Kidney toxicity was observed in studies in male mice and rats; findings in urinary bladder were observed in male mice.

In male mice, golodirsen was administered weekly for 12 weeks by intravenous injection (0, 12, 120, or 960 mg/kg) or for 26 weeks by subcutaneous injection (0, 120, 300, or 600 mg/kg). In the 12-week study, microscopic findings in kidney (tubular dilatation, basophilic or eosinophilic casts, vacuolation), correlated with increases in serum markers of renal function (e.g., urea nitrogen, creatinine), were observed primarily at the highest dose tested; hypertrophy of the transitional epithelium of the ureter or urinary bladder was observed at all doses. In the 26-week study, renal tubular degeneration and degeneration of the transitional epithelium of the urinary bladder were observed at all doses.

In male rats, intravenous administration of golodirsen (0, 60, 100, 300, or 600 mg/kg) weekly for 13 weeks resulted in tubular degeneration at all but the lowest dose tested; at the high dose, the microscopic changes were accompanied by increases in serum urea nitrogen.

In male monkeys, intravenous administration of golodirsen (0, 80, 200, or 400 mg/kg) weekly for 39 weeks resulted in microscopic changes in kidney (basophilia, dilatation, or mononuclear cell infiltration) at all doses, which correlated with increases in serum markers of renal function (urea nitrogen, creatinine) at the highest dose tested.

14 CLINICAL STUDIES

The effect of VYONDYS 53 on dystrophin production was evaluated in one study in DMD patients with a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping (Study 1; NCT02310906).

Study 1 Part 1 was a double-blind, placebo-controlled, dose-titration study in 12 DMD patients. Patients were randomized 2:1 to receive VYONDYS 53 or matching placebo. VYONDYS 53-treated patients received four escalating dose levels, ranging from 4 mg/kg/week (less than the recommended dosage) to 30 mg/kg/week by intravenous infusion for 2 weeks at each dose level.

Study 1 Part 2 was a 168-week, open-label study assessing the efficacy and safety of VYONDYS 53 at a dose of 30 mg/kg/week in the 12 patients enrolled in Part 1, plus 13 additional treatment-naïve patients with DMD amenable to exon 53 skipping. At study entry (either in Part 1 or Part 2), patients had a median age of 8 years and were on a stable dose of corticosteroids for at least 6 months. Efficacy was assessed based on change from baseline in the dystrophin protein level (measured as % of the dystrophin level in healthy subjects, i.e., % of normal) at Week 48 of Part 2. Muscle biopsies were obtained at baseline prior to treatment and at Week 48 of Part 2 in all VYONDYS 53-treated patients (n=25) and were analyzed for dystrophin protein level by Western blot. Mean dystrophin levels increased from 0.10% (SD 0.07) of normal at baseline to 1.02% (SD 1.03) of normal by Week 48 of Study 1 Part 2, with a mean change in dystrophin of 0.92% (SD 1.01) of normal levels ($p<0.001$); the median change from baseline was 0.88%.

Individual patient dystrophin levels from Study 1 are shown in Table 2.

Table 2: Dystrophin Expression by Individual Patient From Study 1

Patient Number	Western Blot % Normal Dystrophin			Patient number	Western Blot % Normal Dystrophin		
	Baseline	Part 2 Week 48	Change from baseline		Baseline	Part 2 Week 48	Change from baseline
1	0.08	0.09	0.01	14	0.22	0.28	0.06
2	0.11	0.11	0.01	15	0.14	0.21	0.07
3	0.21	0.22	0.01	16	0.05	0.42	0.37
4	0.05	0.12	0.08	17	0.07	1.03	0.97
5	0.03	0.12	0.09	18	0.02	1.57	1.55
6	0.06	0.14	0.09	19	0.12	1.17	1.05
7	0.12	0.37	0.25	20	0.03	1.72	1.69
8	0.11	1.06	0.95	21	0.11	1.77	1.66
9	0.06	0.54	0.48	22	0.31	4.30	3.99
10	0.05	0.97	0.92	23	0.11	0.36	0.25
11	0.06	1.55	1.49	24	0.03	0.91	0.88
12	0.07	1.91	1.84	25	0.07	1.29	1.22
13	0.10	3.25	3.15				

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

VYONDYS 53 injection is supplied in single dose vials. The solution is a clear to slightly opalescent, colorless liquid.

- Single-dose vials containing 100 mg/2mL (50 mg/mL) NDC 60923-465-02

16.2 Storage and Handling

Store VYONDYS 53 at 2°C to 8°C (36°F to 46°F). Do not freeze. Store in original carton until ready for use to protect from light.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions

Advise patients and/or caregivers that hypersensitivity reactions, including rash, pyrexia, pruritus, urticaria, dermatitis, and skin exfoliation have occurred in patients who were treated with VYONDYS 53. Instruct them to seek immediate medical care should they experience signs and symptoms of hypersensitivity [*see Warnings and Precautions (5.1)*].

Renal Toxicity

Inform patients nephrotoxicity has occurred with drugs similar to VYONDYS 53. Advise patients of the importance of monitoring for renal toxicity by their healthcare providers during treatment with VYONDYS 53 [*see Warnings and Precautions (5.2)*].

Manufactured for:
Sarepta Therapeutics, Inc.
Cambridge, MA 02142 USA

ATTACHMENT D



NDA 211970

ACCELERATED APPROVAL

Sarepta Therapeutics, Inc.
Attention: Patrick O'Malley
Executive Director, Regulatory Affairs
215 First Street, Suite 415
Cambridge, MA 02142

Dear Mr. O'Malley:

Please refer to your new drug application (NDA) dated December 19, 2018, received December 19, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vyondys 53 (golodirsen) injection, 50 mg per mL.

We acknowledge receipt of your amendment dated November 27, 2019, which constituted a complete response to our August 19, 2019, action letter.

This new drug application provides for the use of Vyondys 53 (golodirsen) injection for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.

APPROVAL AND LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information). Information on submitting SPL files using eLIST may be found

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

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in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on April 15, 2019, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 211970.**" Approval of this submission by FDA is not required before the labeling is used.

EXPIRY DATING PERIOD

An expiration dating period of 24 months is established for the drug product when stored refrigerated (5°C ± 3°C).

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV NDA 211970. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher:

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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marked, "Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher."

- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.
- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.
- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:
 - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
 - the estimated demand in the U.S. for the product, and
 - the actual amount of product distributed in the U.S.

You may also review the requirements related to this program by visiting FDA's Rare Pediatric Disease Priority Review Voucher Program web page.³

ADVISORY COMMITTEE

Your application for Vyondys 53 was not referred to an FDA advisory committee because the safety profile of golodirsen is acceptable, the clinical trial design is acceptable, and the findings on the surrogate marker are clear.

³ <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/RarePediatricDiseasePriorityVoucherProgram/default.htm>

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ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated November 27, 2019. This requirement, along with required completion dates, is listed below.

- 3690-1 In order to verify the clinical benefit of golodirsen, complete Study 4045-301, A Double-Blind, Placebo-Controlled, Multicenter Study With an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients With Duchenne Muscular Dystrophy. The study includes a randomized, double-blind, placebo-controlled period of 96 weeks, and concludes after an open-label extension period to 144 weeks. The primary endpoint will be the 6-minute walk test.

Draft Protocol Submission: 11/2015 (submitted)

Final Protocol Submission: 03/2019 (submitted)

Trial Completion: 04/2024

Final Report Submission: 10/2024

Submit clinical protocols to your IND 119982 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of carcinogenicity, unexpected serious risk of immunogenicity, or an unexpected serious risk of QT prolongation on the ECG.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

3690-2 A two-year carcinogenicity study of intravenously administered golodirsén in rat.

The timetable you submitted on December 4, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 12/2019
Final Protocol Submission: 01/2020
Study Completion: 01/2022
Final Report Submission: 08/2022

3690-3 A 26-week carcinogenicity study of golodirsén, administered by a clinically relevant route, in an appropriate transgenic mouse model.

The timetable you submitted on December 4, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 12/2019
Final Protocol Submission: 01/2020
Study Completion: 07/2020
Final Report Submission: 02/2021

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- 3690-4 Evaluate patient immune responses, including IgM and IgG isotypes to dystrophin, among patients treated with golodirsen in Study 4053-101 of the clinical development program. Test the samples, collected to detect early, peak, and late antibody responses, using fully validated anti-dystrophin assays that detect IgG and IgM antibodies. Test samples that are positive for antibodies to dystrophin for titer. Determine the impact of immune responses on product pharmacokinetics and clinical efficacy and safety.

The timetable you submitted on December 4, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 05/2017 (submitted)
Study Completion: 10/2019
Final Report Submission: 12/2019

- 3690-5 Evaluate patient immune responses to golodirsen among patients treated with golodirsen in Study 4053-101 of the clinical development program. Test the samples, collected to detect antibody responses, using a fully validated assay that detects IgG and IgM antibody isotypes. Test samples that are positive for antibodies to golodirsen for titer and neutralizing activity using fully validated assays. Until these assays have been fully validated and reviewed by FDA, sufficient samples should be banked and stored under appropriate conditions. Determine the impact of immune responses on product pharmacokinetics and clinical efficacy and safety.

The timetable you submitted on December 4, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 05/2017 (submitted)
Study Completion: 10/2019
Bridge Assay Validation Final Report: 12/2019
Neutralizing Antibody Validation Assay Final Report: 07/2020
Final Report Submission: 12/2020

- 3690-6 Evaluate the immunogenicity of golodirsen-induced truncated dystrophin protein. Assess the immunogenicity risk of any novel epitopes that will be present in the golodirsen-induced truncated dystrophin protein. This can be done in silico or in vitro. If there are novel epitopes that could increase the immunogenicity risk, evaluate the immunogenicity of golodirsen-induced truncated dystrophin protein in the corresponding subjects.

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The timetable you submitted on December 4, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 12/2019
Final Protocol Submission: 02/2020
Epitope Analysis Report Submission: 04/2020
Study Completion: 04/2020
Final Report Submission: 08/2020

3690-7 Submit ECG data from Study 4045-301 to support your request to waive a thorough QT study. If these data do not support a TQT study waiver, you will need to evaluate the effect of golodirsen on the QTc interval in a dedicated study as per the ICH E14 guideline.

The timetable you submitted on December 4, 2019, states that you will conduct this study according to the following schedule:

Study Completion: 04/2024
Final Report Submission: 10/2024

Submit clinical protocol(s) to your IND 119982 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:
Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

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ENHANCED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance for serious renal toxicity events and for rhabdomyolysis. Provide expedited reporting of serious renal toxicity events and of rhabdomyolysis, and provide comprehensive summaries and analyses of these events as part of your required postmarketing safety reports [e.g., periodic safety update reports (PSURs)]. In the analysis of each case, provide an assessment of causality, with documentation of risk factors and results of all assessments that support the diagnosis or the causality, along with duration of Vyondys 53 therapy, the time from first Vyondys 53 dose to adverse event onset, the time from last Vyondys 53 dose prior to the event onset, concomitant therapies, treatment given for the event, and outcome. Include a comparison of the rates of renal failure, glomerulonephritis, and rhabdomyolysis to background rates of those events in the general population (overall and stratified by age), as well as background rates (if available) for patients with Duchenne muscular dystrophy (DMD) (overall and stratified by age).

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information (PI)/Medication Guide/Patient Package Insert (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

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Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.⁴

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.⁵

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

⁴ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁵ <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>

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If you have any questions, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Billy Dunn, M.D.
Director (Acting)
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
 - Prescribing Information

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM H Dunn
12/12/2019 04:43:55 PM

ATTACHMENT E

37247



US00994851B2

(12) **United States Patent**
Wilton et al.(10) **Patent No.:** **US 9,994,851 B2**
(45) **Date of Patent:** ***Jun. 12, 2018**(54) **ANTISENSE OLIGONUCLEOTIDES FOR
INDUCING EXON SKIPPING AND
METHODS OF USE THEREOF**(71) Applicant: **The University of Western Australia,**
Crawley (AU)(72) Inventors: **Stephen Donald Wilton, Applecross**
(AU); Sue Fletcher, Bayswater (AU);
Graham McClorey, Bayswater (AU)(73) Assignee: **The University of Western Australia,**
Crawley (AU)(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days. days.

This patent is subject to a terminal dis-
claimer.(21) Appl. No.: **15/705,172**(22) Filed: **Sep. 14, 2017**(65) **Prior Publication Data**

US 2018/0002697 A1 Jan. 4, 2018

Related U.S. Application Data(63) Continuation of application No. 15/274,772, filed on
Sep. 23, 2016, which is a continuation of application
No. 14/740,097, filed on Jun. 15, 2015, now Pat. No.
9,605,262, which is a continuation of application No.
13/741,150, filed on Jan. 14, 2013, now abandoned,
which is a continuation of application No.
13/168,857, filed on Jun. 24, 2011, now abandoned,
which is a continuation of application No.
12/837,359, filed on Jul. 15, 2010, now Pat. No.
8,232,384, which is a continuation of application No.
11/570,691, filed as application No.
PCT/AU2005/000943 on Jun. 28, 2005, now Pat. No.
7,807,816.(30) **Foreign Application Priority Data**

Jun. 28, 2004 (AU) 2004903474

(51) **Int. Cl.****C07H 21/04** (2006.01)**C12N 15/113** (2010.01)(52) **U.S. Cl.**CPC **C12N 15/113** (2013.01); **C12N 2310/11**
(2013.01); **C12N 2310/315** (2013.01); **C12N**
2310/321 (2013.01); **C12N 2310/3233**
(2013.01); **C12N 2310/33** (2013.01); **C12N**
2310/3341 (2013.01); **C12N 2310/3519**
(2013.01); **C12N 2320/30** (2013.01); **C12N**
2320/33 (2013.01)(58) **Field of Classification Search**CPC **C07H 21/04**
See application file for complete search history.(56) **References Cited****U.S. PATENT DOCUMENTS**4,458,066 A 7/1984 Caruthers et al.
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OTHER PUBLICATIONS"Efficacy Study of AVI-4658 to Induce Dystrophin Expression in
Selected Duchenne Muscular Dystrophy Patients" ClinicalTrials.
gov dated Jan. 22, 2013.

(Continued)

Primary Examiner — Kimberly Chong

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(57)

ABSTRACTAn antisense molecule capable of binding to a selected target
site to induce exon skipping in the dystrophin gene, as set
forth in SEQ ID NO: 1 to 214.**2 Claims, 22 Drawing Sheets**

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106	c		
107	a		
108	g		
109	c		
110	a		
111	g		
112	c		
113	a		
114	g		
115	c		
116	a		
117	g		
118	c		
119	a		
120	g		
121	c		
122	a		
123	g		
124	c		
125	a		
126	g		
127	c		
128	a		
129			

SEQ ID NO:213

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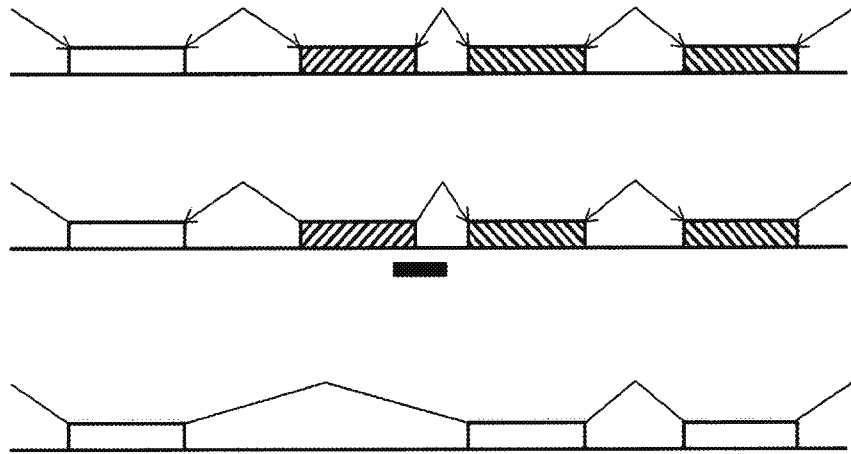
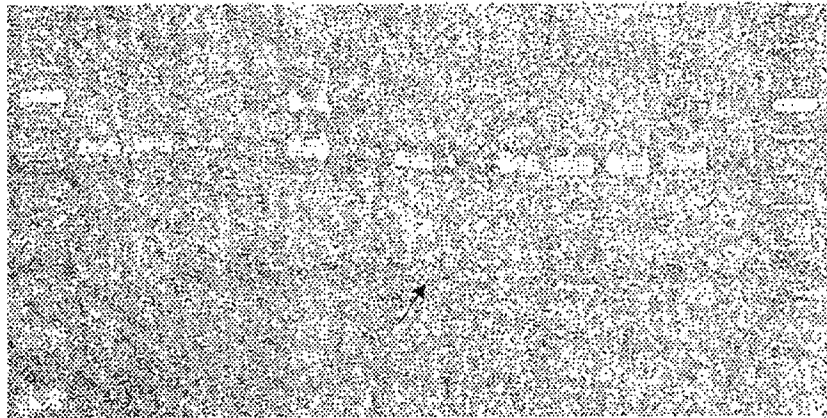


FIGURE 2

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H8A(-06+14) | H8A(-06+18)
M 600 300 100 50 20 UT 600 300 100 50 20 UT M

**FIGURE 3**

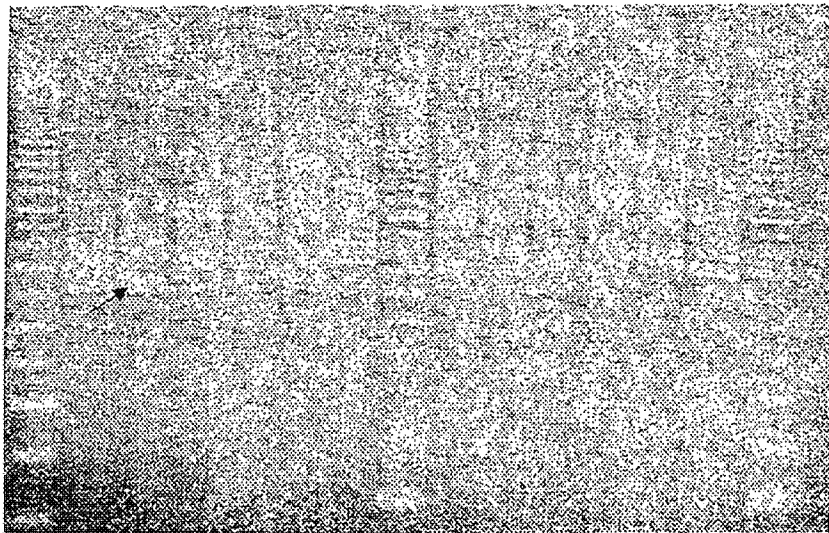
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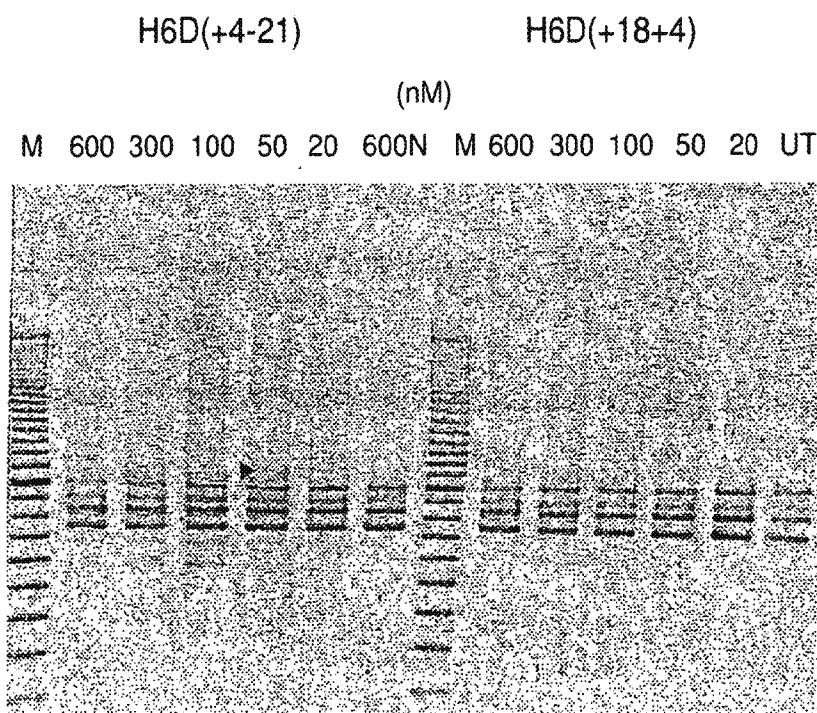
H7A(+45+67) H7A(+2+26)
M 600 300 100 50 20 600NM 600 300 100 50 20 600N M

**FIGURE 4**

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US 9,994,851 B2**FIGURE 5**

U.S. Patent

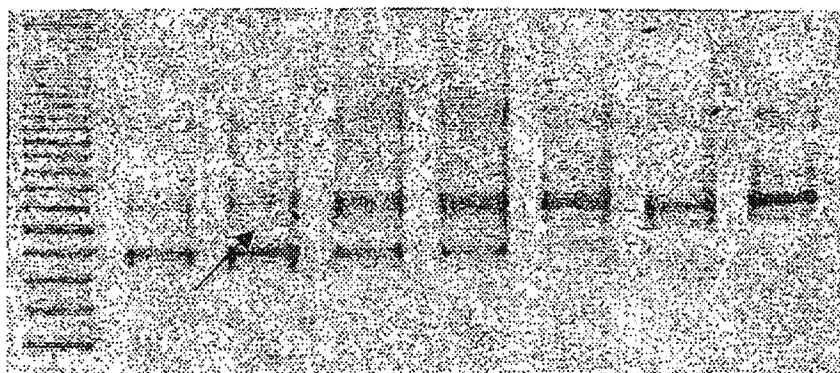
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6A(+69+91)

M 600 300 200 100 50 20 UT

**FIGURE 6**

U.S. Patent

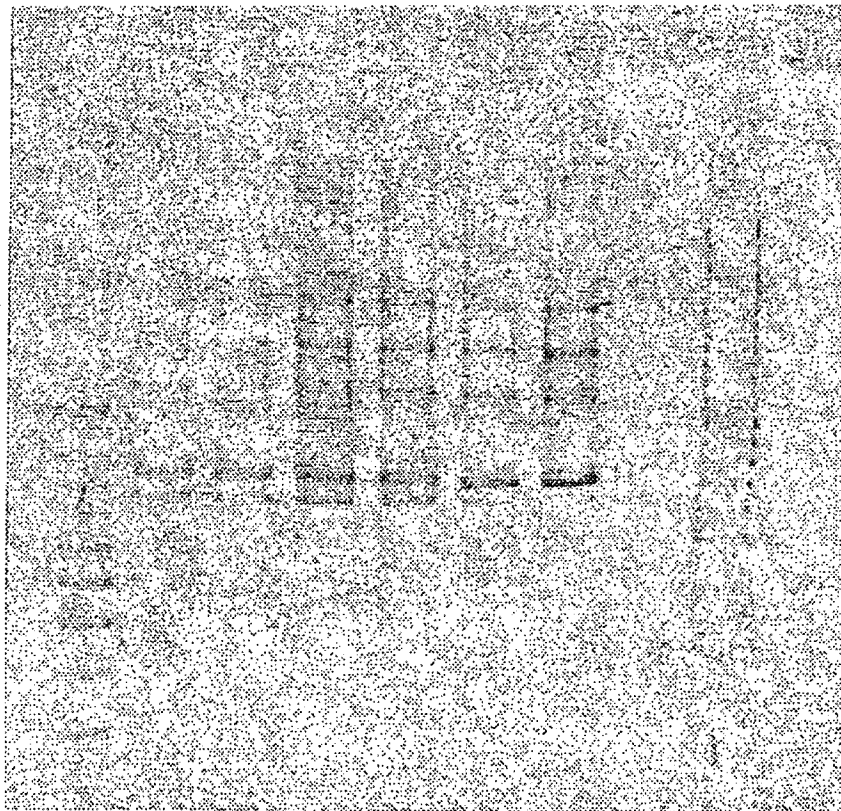
Jun. 12, 2018

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H4A(+13+32)

M 600 300 100 50 20 UT Neg M

**FIGURE 7**

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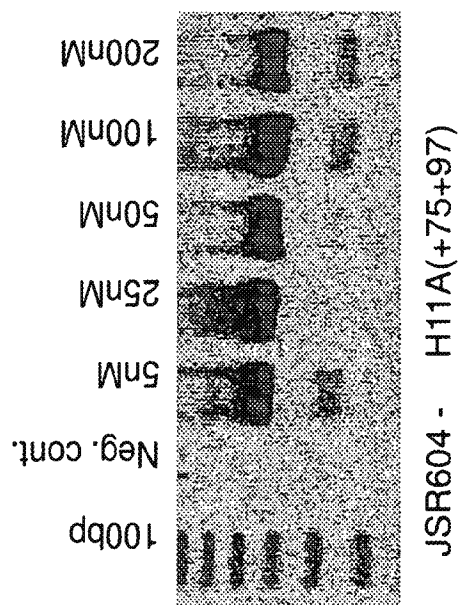


FIGURE 8B

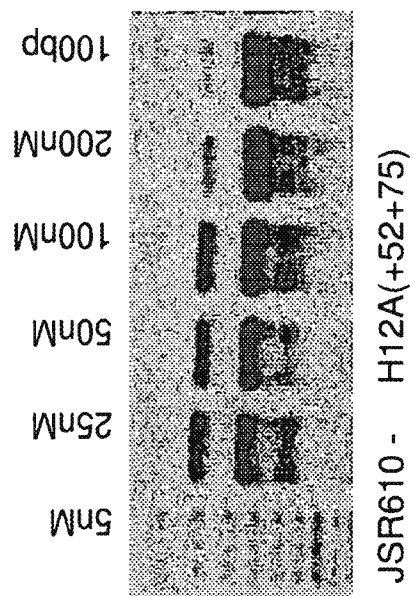


FIGURE 8A

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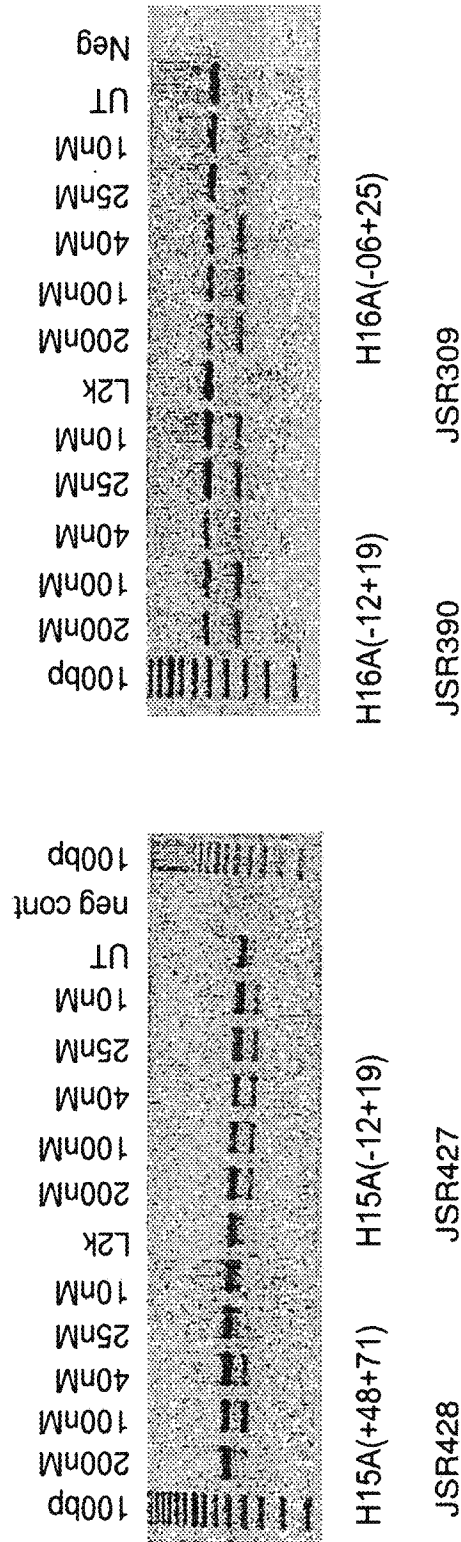


FIGURE 9A

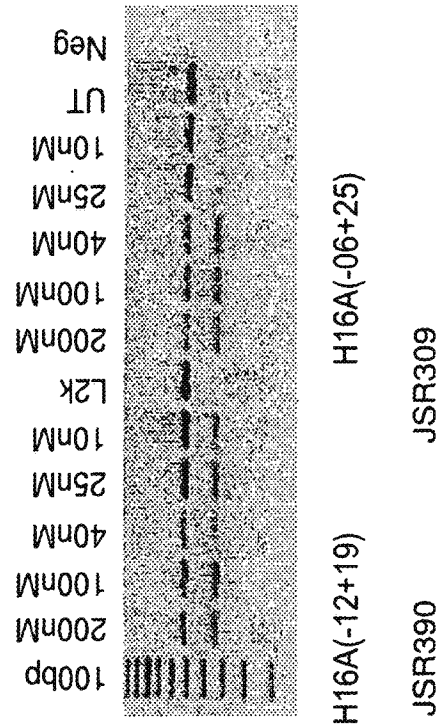


FIGURE 9B

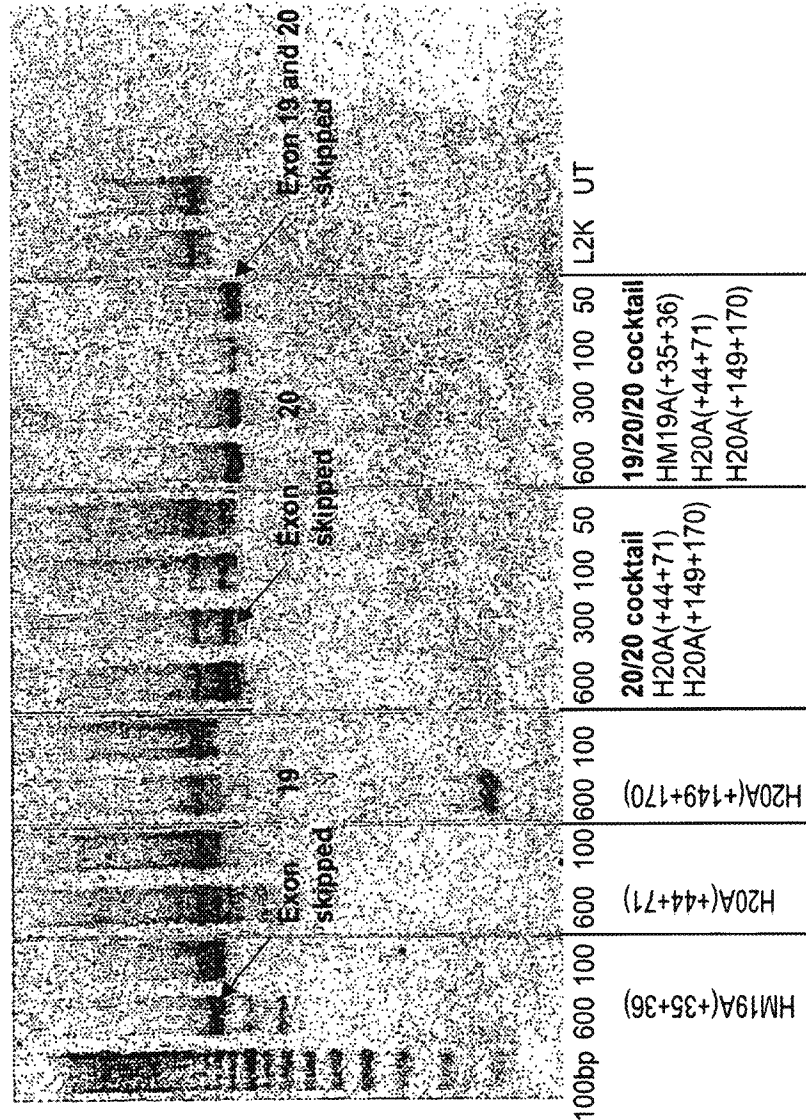


FIGURE 10

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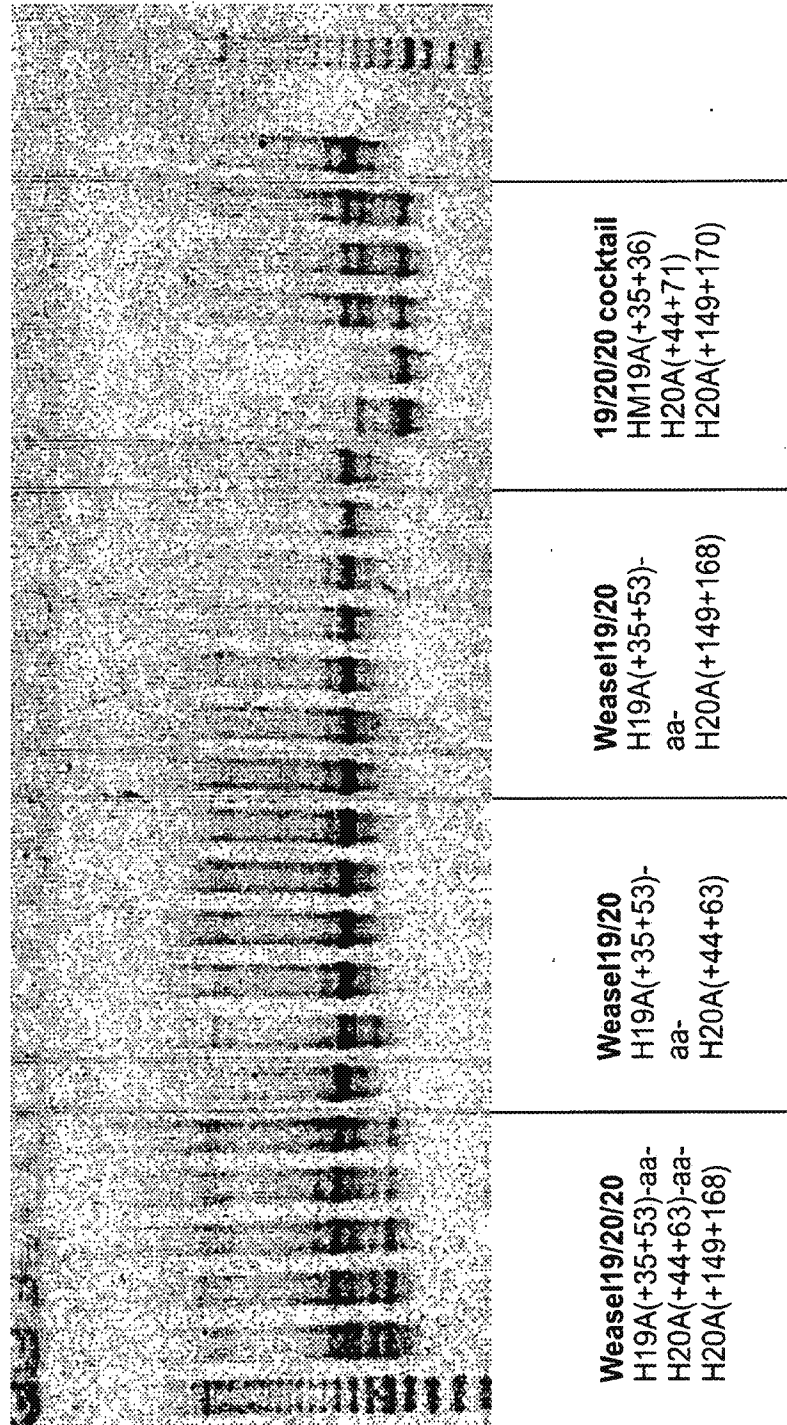


FIGURE 11

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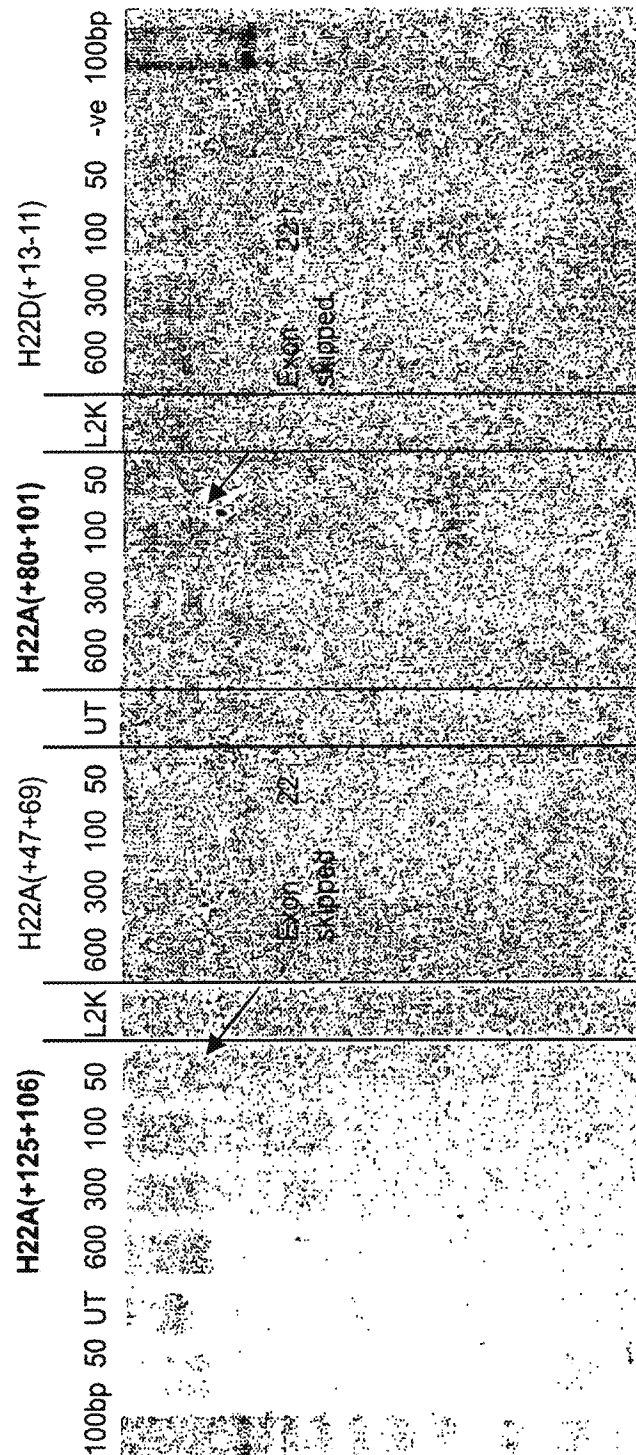


FIGURE 12

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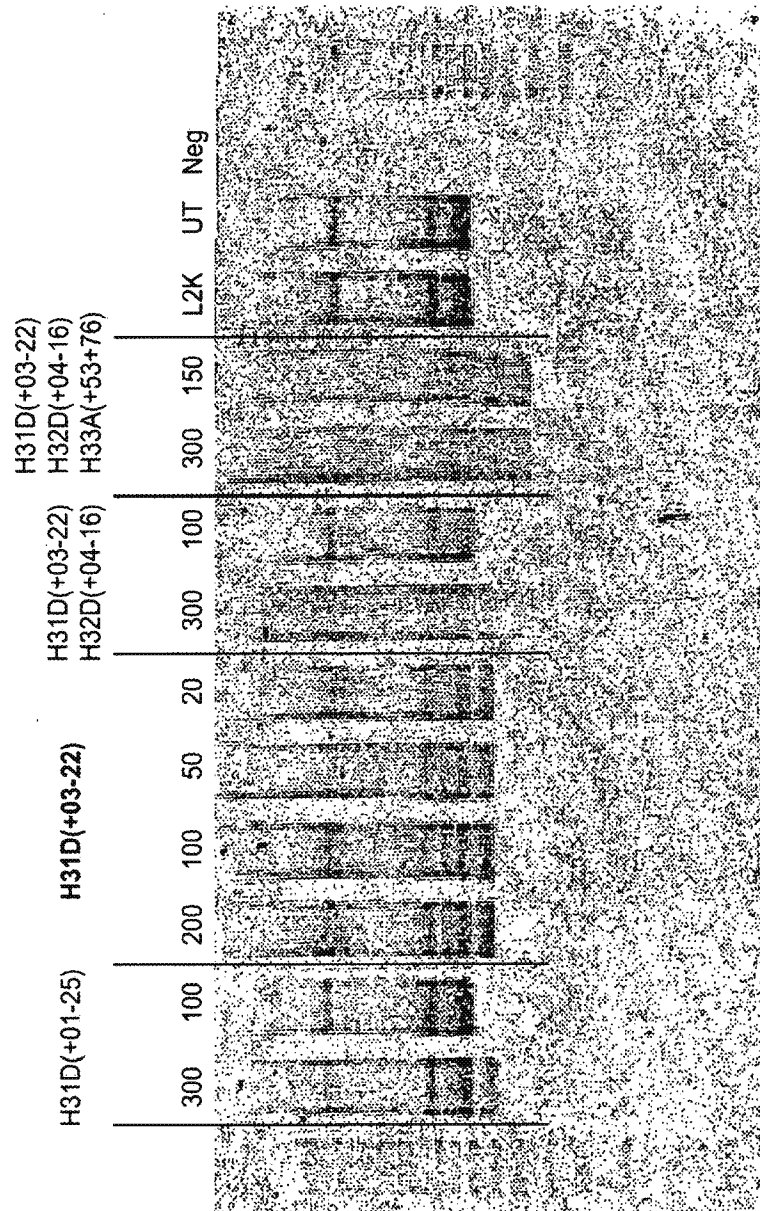


FIGURE 13

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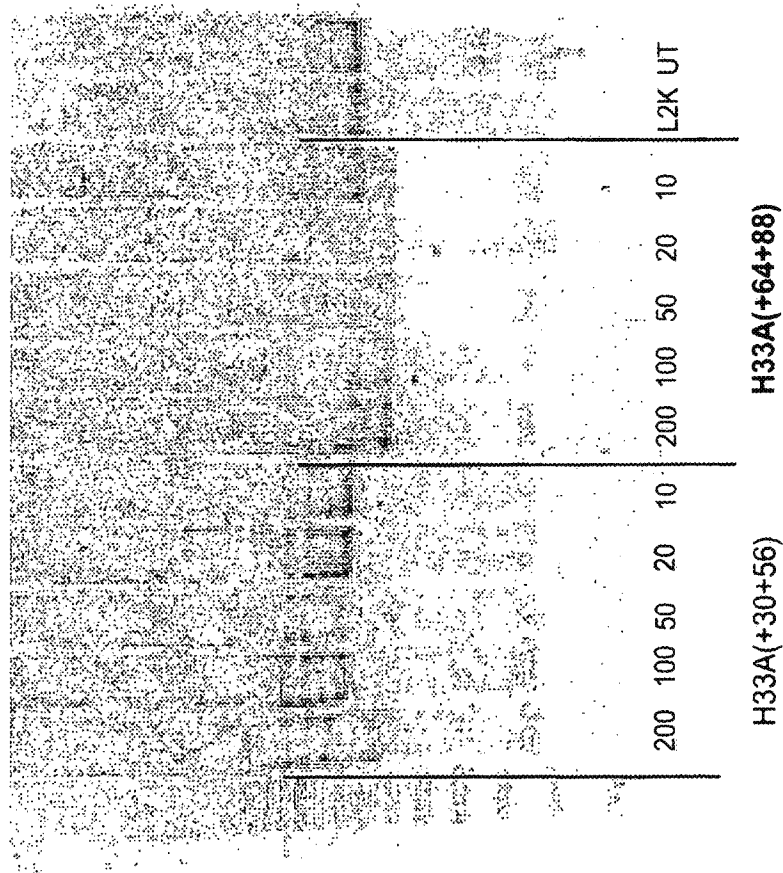


FIGURE 14

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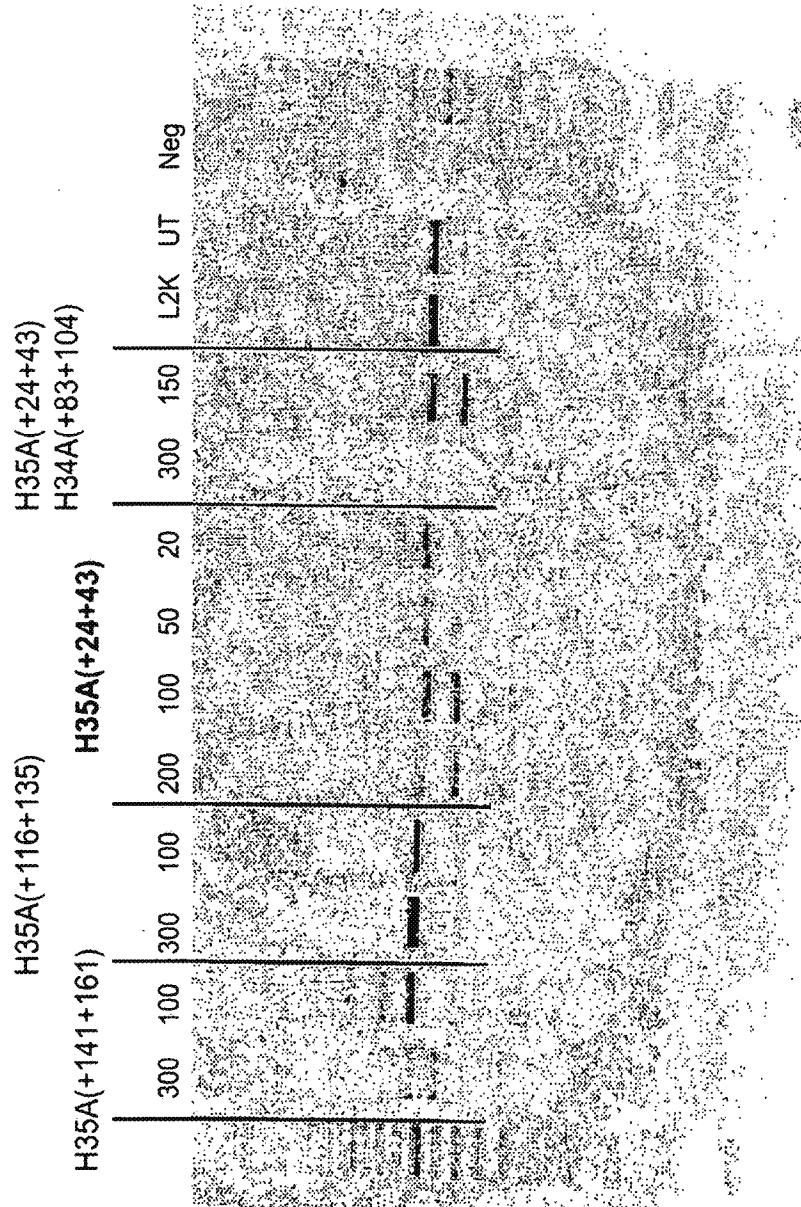
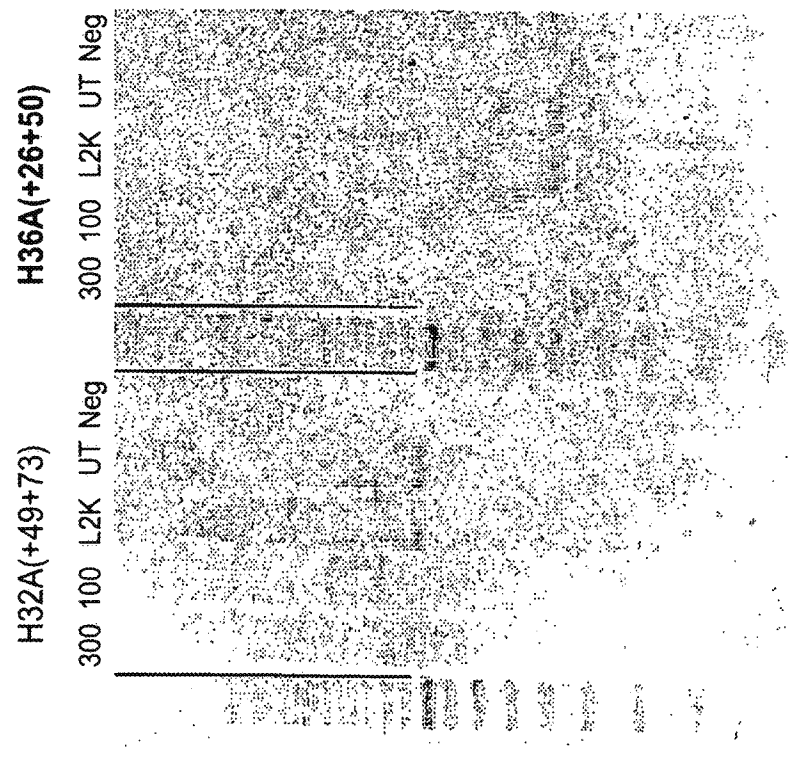


FIGURE 15

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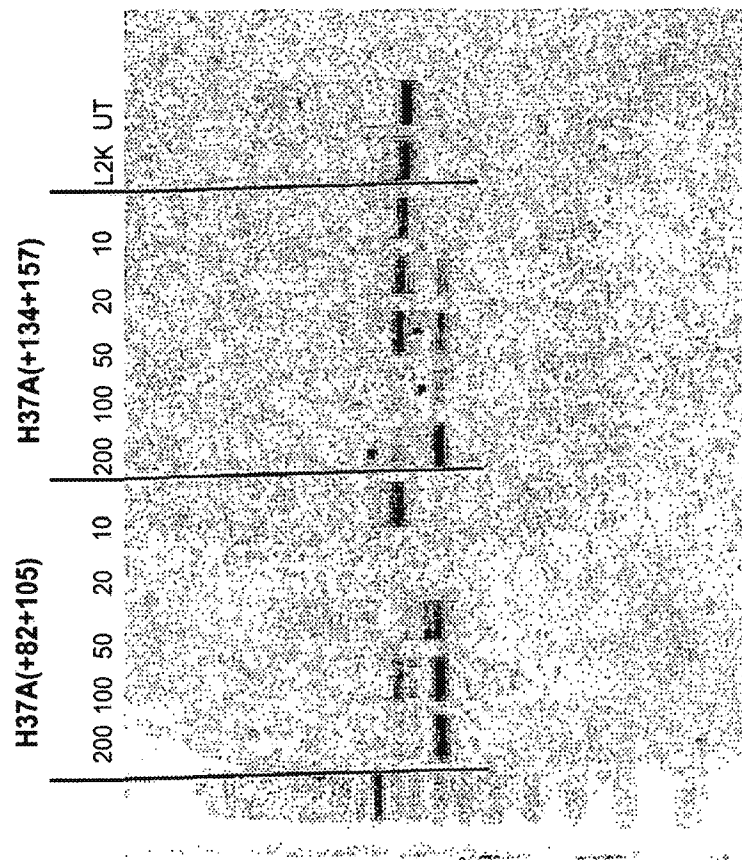
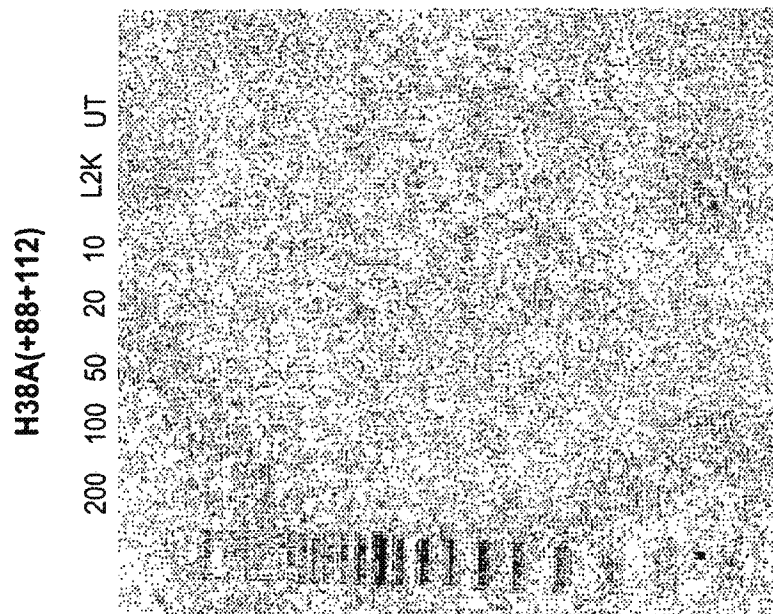


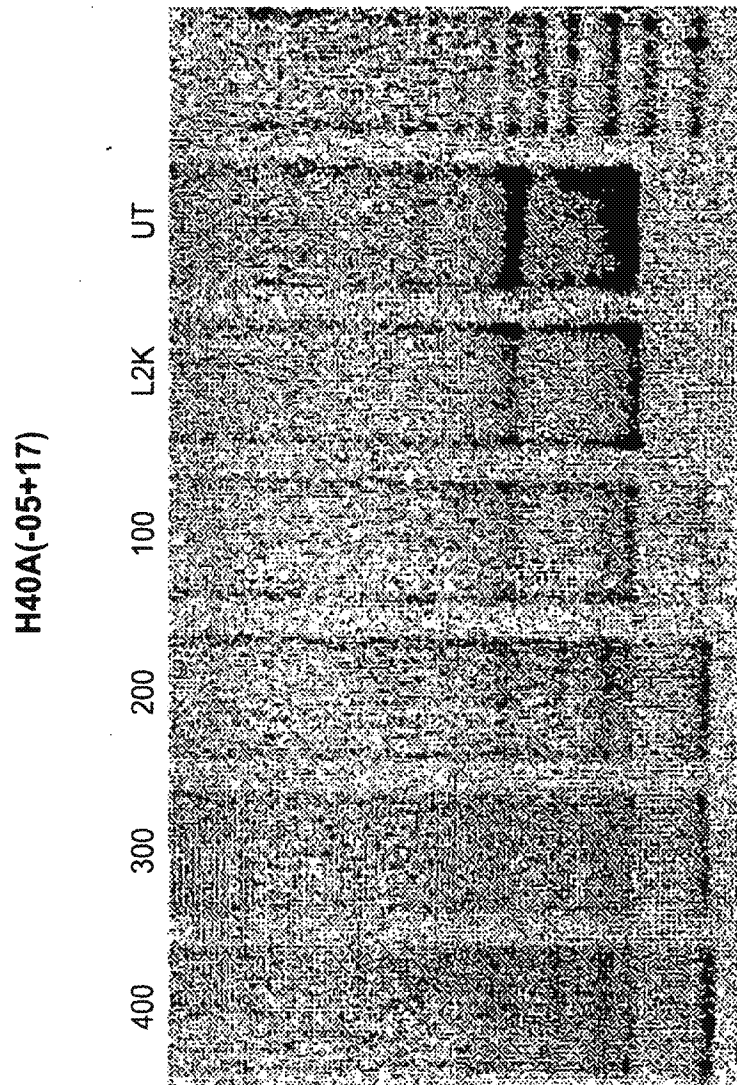
FIGURE 17

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US 9,994,851 B2**FIGURE 19**

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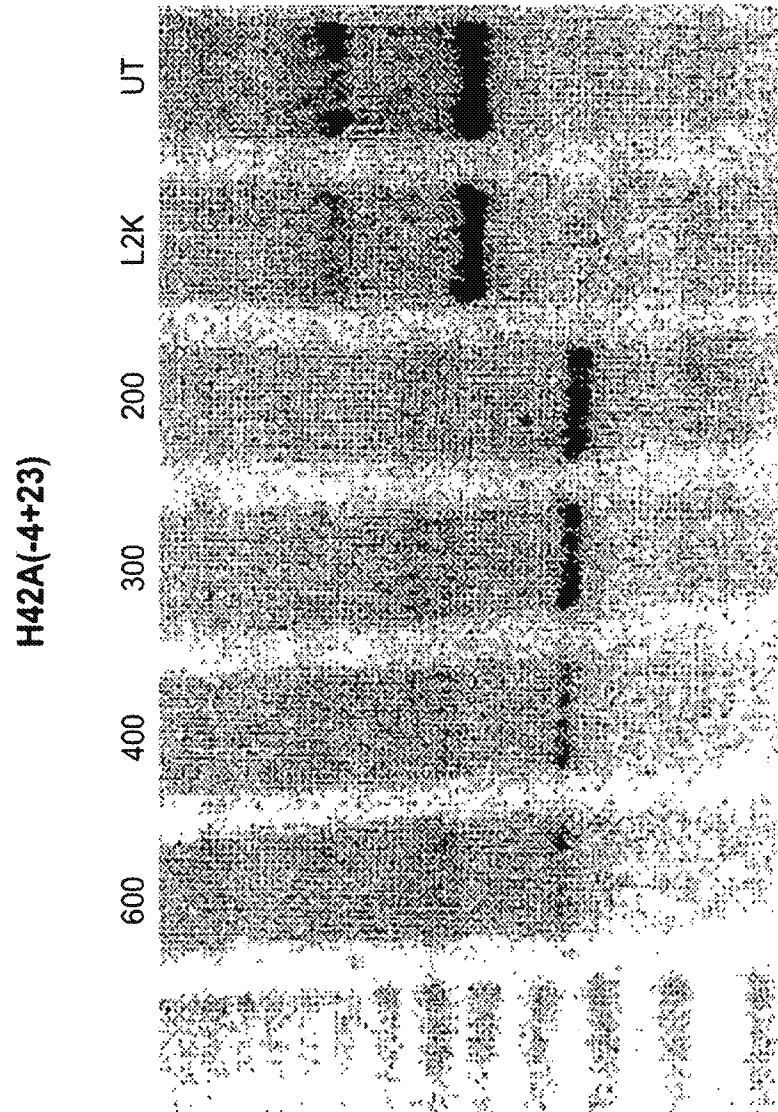
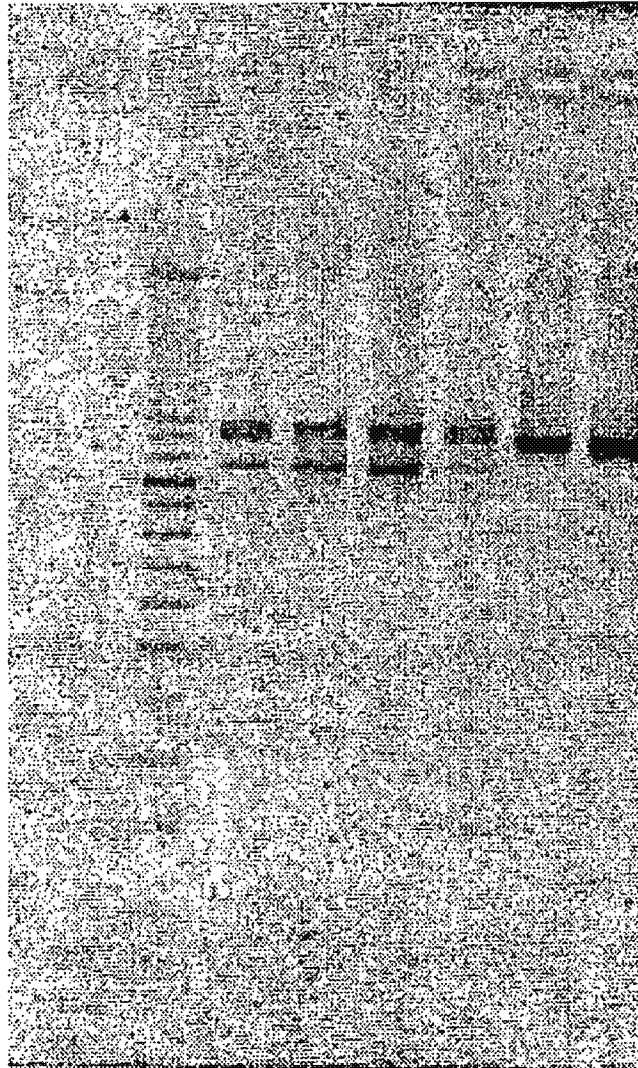


FIGURE 20

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600 300 200 100 L2K UT

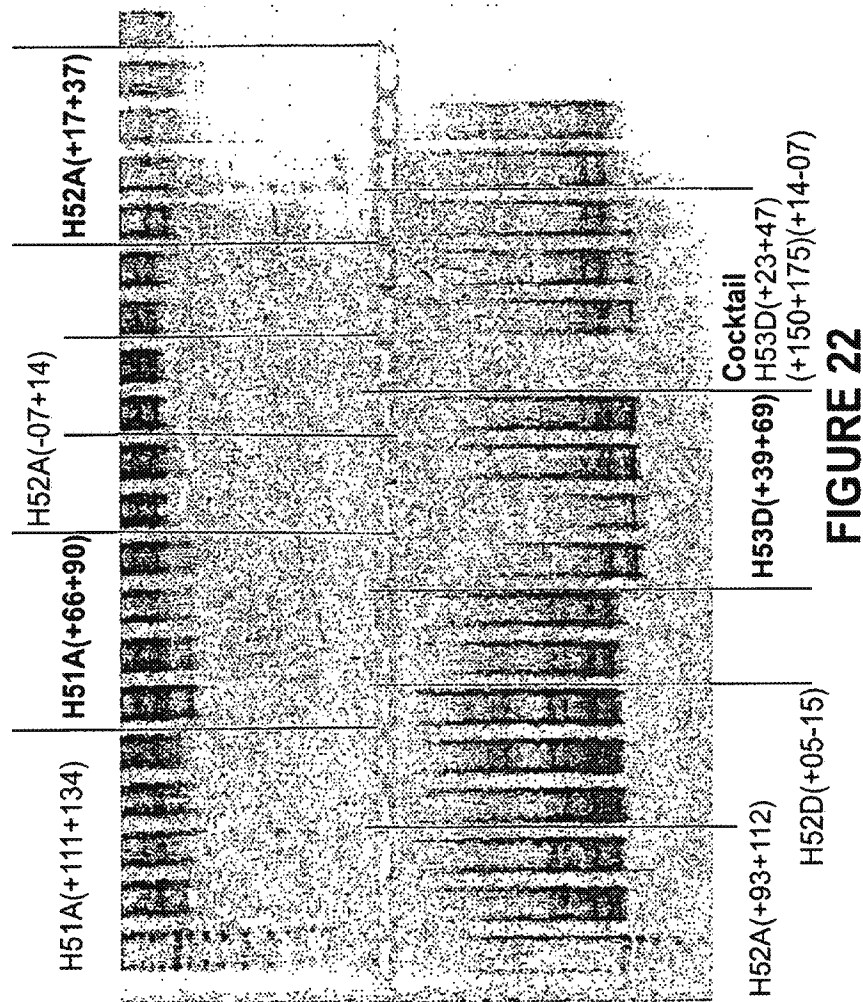
**FIGURE 21**

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ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 15/274,772, filed Sep. 23, 2016, now pending, which application is a continuation of U.S. patent application Ser. No. 14/740,097, filed Jun. 15, 2015, now issued as U.S. Pat. No. 9,605,262, which application is a continuation of U.S. patent application Ser. No. 13/741,150, filed Jan. 14, 2013, now abandoned, which application is a continuation of U.S. patent application Ser. No. 13/168,857, filed Jun. 24, 2011, now abandoned, which application is a continuation of U.S. patent application Ser. No. 12/837,359, filed Jul. 15, 2010, now issued as U.S. Pat. No. 8,232,384, which application is a continuation of U.S. patent application Ser. No. 11/570,691, filed Jan. 15, 2008, now issued as U.S. Pat. No. 7,807,816, which application is a 35 U.S.C. § 371 National Phase Application of PCT/AU2005/000943, filed Jun. 28, 2005, which claims priority to Australian Patent Application No. 2004903474, filed Jun. 28, 2004; which applications are each incorporated herein by reference in their entireties.

STATEMENT REGARDING SEQUENCE LISTING

The Sequence Listing associated with the application is provided in text format in lieu of a paper copy, and is hereby incorporated by reference into the specification. The name of the text file containing the Sequence Listing is AVN-008CN41_Sequence-Listing.txt. The text file is 62,086 Kilobytes, was created on Sep. 14, 2017 and is being submitted electronically via EFS-Web.

FIELD OF THE INVENTION

The present invention relates to novel antisense compounds and compositions suitable for facilitating exon skipping. It also provides methods for inducing exon skipping using the novel antisense compounds as well as therapeutic compositions adapted for use in the methods of the invention.

BACKGROUND ART

Significant effort is currently being expended researching methods for suppressing or compensating for disease-causing mutations in genes. Antisense technologies are being developed using a range of chemistries to affect gene expression at a variety of different levels (transcription, splicing, stability, translation). Much of that research has focused on the use of antisense compounds to correct or compensate for abnormal or disease-associated genes in a myriad of different conditions.

Antisense molecules are able to inhibit gene expression with exquisite specificity and because of this many research efforts concerning oligonucleotides as modulators of gene expression have focused on inhibiting the expression of targeted genes such as oncogenes or viral genes. The antisense oligonucleotides are directed either against RNA (sense strand) or against DNA where they form triplex structures inhibiting transcription by RNA polymerase II. To achieve a desired effect in specific gene down-regulation, the oligonucleotides must either promote the decay of the tar-

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geted mRNA or block translation of that mRNA, thereby effectively preventing de novo synthesis of the undesirable target protein.

Such techniques are not useful where the object is to up-regulate production of the native protein or compensate for mutations which induce premature termination of translation such as nonsense or frame-shifting mutations. Furthermore, in cases where a normally functional protein is prematurely terminated because of mutations therein, a means for restoring some functional protein production through antisense technology has been shown to be possible through intervention during the splicing processes (Sierakowska H, et al., (1996) *Proc Natl Acad Sci USA* 93, 12840-12844; Wilton S D, et al., (1999) *Neuromusc Disorders* 9, 330-338; van Deutekom J C et al., (2001) *Human Mol Genet* 10, 1547-1554). In these cases, the defective gene transcript should not be subjected to targeted degradation so the antisense oligonucleotide chemistry should not promote target mRNA decay.

In a variety of genetic diseases, the effects of mutations on the eventual expression of a gene can be modulated through a process of targeted exon skipping during the splicing process. The splicing process is directed by complex multiparticle machinery that brings adjacent exon-intron junctions in pre-mRNA into close proximity and performs cleavage of phosphodiester bonds at the ends of the introns with their subsequent reformation between exons that are to be spliced together. This complex and highly precise process is mediated by sequence motifs in the pre-mRNA that are relatively short semi-conserved RNA segments to which bind the various nuclear splicing factors that are then involved in the splicing reactions. By changing the way the splicing machinery reads or recognises the motifs involved in pre-mRNA processing, it is possible to create differentially spliced mRNA molecules. It has now been recognised that the majority of human genes are alternatively spliced during normal gene expression, although the mechanisms invoked have not been identified. Using antisense oligonucleotides, it has been shown that errors and deficiencies in a coded mRNA could be bypassed or removed from the mature gene transcripts.

In nature, the extent of genetic deletion or exon skipping in the splicing process is not fully understood, although many instances have been documented to occur, generally at very low levels (Sherrat T G, et al., (1993) *Am J Hum Genet* 53, 1007-1015). However, it is recognised that if exons associated with disease-causing mutations can be specifically deleted from some genes, a shortened protein product can sometimes be produced that has similar biological properties of the native protein or has sufficient biological activity to ameliorate the disease caused by mutations associated with the target exon (Lu Q L, et al., (2003) *Nature Medicine* 9, 1009-1014; Aartsma-Rus A et al., (2004) *Am J Hum Genet* 74: 83-92).

This process of targeted exon skipping is likely to be particularly useful in long genes where there are many exons and introns, where there is redundancy in the genetic constitution of the exons or where a protein is able to function without one or more particular exons (e.g. with the dystrophin gene, which consists of 79 exons; or possibly some collagen genes which encode for repeated blocks of sequence or the huge nebulin or titin genes which are comprised of ~80 and over 370 exons, respectively).

Efforts to redirect gene processing for the treatment of genetic diseases associated with truncations caused by mutations in various genes have focused on the use of antisense oligonucleotides that either: (1) fully or partially overlap

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with the elements involved in the splicing process; or (2) bind to the pre-mRNA at a position sufficiently close to the element to disrupt the binding and function of the splicing factors that would normally mediate a particular splicing reaction which occurs at that element (e.g., binds to the pre-mRNA at a position within 3, 6, or 9 nucleotides of the element to be blocked).

For example, modulation of mutant dystrophin pre-mRNA splicing with antisense oligoribonucleotides has been reported both in vitro and in vivo. In one type of dystrophin mutation reported in Japan, a 52-base pair deletion mutation causes exon 19 to be removed with the flanking introns during the splicing process (Matsuo et al., (1991) *J Clin Invest.*, 87:2127-2131). An in vitro minigene splicing system has been used to show that a 31-mer 2'-O-methyl oligoribonucleotide complementary to the 5' half of the deleted sequence in dystrophin Kobe exon 19 inhibited splicing of wild-type pre-mRNA (Takeshima et al. (1995), *J. Clin. Invest.*, 95, 515-520). The same oligonucleotide was used to induce exon skipping from the native dystrophin gene transcript in human cultured lymphoblastoid cells.

Dunckley et al., (1997) *Nucleosides & Nucleotides*, 16, 1665-1668 described in vitro constructs for analysis of splicing around exon 23 of mutated dystrophin in the mdx mouse mutant, a model for muscular dystrophy. Plans to analyse these constructs in vitro using 2' modified oligonucleotides targeted to splice sites within and adjacent to mouse dystrophin exon 23 were discussed, though no target sites or sequences were given.

2'-O-methyl oligoribonucleotides were subsequently reported to correct dystrophin deficiency in myoblasts from the mdx mouse from this group. An antisense oligonucleotide targeted to the 3' splice site of murine dystrophin intron 22 was reported to cause skipping of the mutant exon as well as several flanking exons and created a novel in-frame dystrophin transcript with a novel internal deletion. This mutated dystrophin was expressed in 1-2% of antisense treated mdx myotubes. Use of other oligonucleotide modifications such as 2'-O-methoxyethyl phosphodiester are described (Dunckley et al. (1998) *Human Mol. Genetics*, 5, 1083-90).

Thus, antisense molecules may provide a tool in the treatment of genetic disorders such as Duchenne Muscular Dystrophy (DMD). However, attempts to induce exon skipping using antisense molecules have had mixed success. Studies on dystrophin exon 19, where successful skipping of that exon from the dystrophin pre-mRNA was achieved using a variety of antisense molecules directed at the flanking splice sites or motifs within the exon involved in exon definition as described by Errington et al. (2003) *J Gen Med* 5, 518-527".

In contrast to the apparent ease of exon 19 skipping, the first report of exon 23 skipping in the mdx mouse by Dunckley et al., (1998) is now considered to be reporting only a naturally occurring revertant transcript or artefact rather than any true antisense activity. In addition to not consistently generating transcripts missing exon 23, Dunckley et al., (1998) did not show any time course of induced exon skipping, or even titration of antisense oligonucleotides, to demonstrate dose dependent effects where the levels of exon skipping corresponded with increasing or decreasing amounts of antisense oligonucleotide. Furthermore, this work could not be replicated by other researchers.

The first example of specific and reproducible exon skipping in the mdx mouse model was reported by Wilton et al., (1999) *Neuromuscular Disorders* 9, 330-338. By directing an antisense molecule to the donor splice site, consistent and efficient exon 23 skipping was induced in the dystrophin mRNA within 6 hours of treatment of the cultured cells. Wilton et al, (1999), also describe targeting the acceptor

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region of the mouse dystrophin pre-mRNA with longer antisense oligonucleotides and being unable to repeat the published results of Dunckley et al., (1998). No exon skipping, either 23 alone or multiple removal of several flanking exons, could be reproducibly detected using a selection of antisense oligonucleotides directed at the acceptor splice site of intron 22.

While the first antisense oligonucleotide directed at the intron 23 donor splice site induced consistent exon skipping in primary cultured myoblasts, this compound was found to be much less efficient in immortalized cell cultures expressing higher levels of dystrophin. However, with refined targeting and antisense oligonucleotide design, the efficiency of specific exon removal was increased by almost an order of magnitude (see Mann C J et al., (2002) *J Gen Med* 4, 644-654).

Thus, there remains a need to provide antisense oligonucleotides capable of binding to and modifying the splicing of a target nucleotide sequence. Simply directing the antisense oligonucleotides to motifs presumed to be crucial for splicing is no guarantee of the efficacy of that compound in a therapeutic setting.

SUMMARY OF THE INVENTION

The present invention provides antisense molecule compounds and compositions suitable for binding to RNA motifs involved in the splicing of pre-mRNA that are able to induce specific and efficient exon skipping and a method for their use thereof.

The choice of target selection plays a crucial role in the efficiency of exon skipping and hence its subsequent application of a potential therapy. Simply designing antisense molecules to target regions of pre-mRNA presumed to be involved in splicing is no guarantee of inducing efficient and specific exon skipping. The most obvious or readily defined targets for splicing intervention are the donor and acceptor splice sites although there are less defined or conserved motifs including exonic splicing enhancers, silencing elements and branch points.

The acceptor and donor splice sites have consensus sequences of about 16 and 8 bases respectively (see FIG. 1 for schematic representation of motifs and domains involved in exon recognition, intron removal and the splicing process).

According to a first aspect, the invention provides antisense molecules capable of binding to a selected target to induce exon skipping.

For example, to induce exon skipping in exons 3 to 8, 10 to 16, 19 to 40, 42 to 44, 46, 47, and 50 to 53 in the Dystrophin gene transcript the antisense molecules are preferably selected from the group listed in Table 1A.

In a further example, it is possible to combine two or more antisense oligonucleotides of the present invention together to induce multiple exon skipping in exons 19-20, and 53. This is a similar concept to targeting of a single exon. A combination or "cocktail" of antisense oligonucleotides are directed at adjacent exons to induce efficient exon skipping.

In another example, to induce exon skipping in exons 19-20, 31, 34 and 53 it is possible to improve exon skipping of a single exon by joining together two or more antisense oligonucleotide molecules. This concept is termed by the inventor as a "weasel", an example of a cunningly designed antisense oligonucleotide. A similar concept has been described in Aartsma-Rus A et al., (2004) *Am J Hum Genet* 74: 83-92).

According to a second aspect, the present invention provides antisense molecules selected and or adapted to aid in the prophylactic or therapeutic treatment of a genetic disorder comprising at least an antisense molecule in a form suitable for delivery to a patient.

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According to a third aspect, the invention provides a method for treating a patient suffering from a genetic disease wherein there is a mutation in a gene encoding a particular protein and the affect of the mutation can be abrogated by exon skipping, comprising the steps of: (a) selecting an antisense molecule in accordance with the methods described herein; and (b) administering the molecule to a patient in need of such treatment.

The invention also addresses the use of purified and isolated antisense oligonucleotides of the invention, for the manufacture of a medicament for treatment of a genetic disease.

The invention further provides a method of treating a condition characterised by Duchenne muscular dystrophy, which method comprises administering to a patient in need of treatment an effective amount of an appropriately designed antisense oligonucleotide of the invention, relevant to the particular genetic lesion in that patient. Further, the invention provides a method for prophylactically treating a patient to prevent or at least minimise Duchene muscular dystrophy, comprising the step of: administering to the patient an effective amount of an antisense oligonucleotide or a pharmaceutical composition comprising one or more of these biological molecules.

The invention also provides kits for treating a genetic disease, which kits comprise at least a antisense oligonucleotide of the present invention, packaged in a suitable container and instructions for its use.

Other aspects and advantages of the invention will become apparent to those skilled in the art from a review of the ensuing description, which proceeds with reference to the following figures.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 Schematic representation of motifs and domains involved in exon recognition, intron removal and the splicing process (SEQ ID NOS: 213 and 214).

FIG. 2 Diagrammatic representation of the concept of antisense oligonucleotide induced exon skipping to by-pass disease-causing mutations (not drawn to scale). The hatched box represents an exon carrying a mutation that prevents the translation of the rest of the mRNA into a protein. The solid black bar represents an antisense oligonucleotide that prevents inclusion of that exon in the mature mRNA.

FIG. 3 Gel electrophoresis showing differing efficiencies of two antisense molecules directed at exon 8 acceptor splice site. The preferred compound [H8A(-06+18)] induces strong and consistent exon skipping at a transfection concentration of 20 nanomolar in cultured normal human muscle cells. The less preferred antisense oligonucleotide [H8A(-06+14)] also induces efficient exon skipping, but at much higher concentrations. Other antisense oligonucleotides directed at exon 8 either only induced lower levels of exon skipping or no detectable skipping at all (not shown).

FIG. 4 Gel electrophoresis showing differing efficiencies of two antisense molecules directed at internal domains within exon 7, presumably exon splicing enhancers. The preferred compound [H7A(+45+67)] induces strong and consistent exon skipping at a transfection concentration of 20 nanomolar in cultured human muscle cells. The less preferred antisense oligonucleotide [H7A(+2+26)] induces only low levels of exon skipping at the higher transfection concentrations. Other antisense oligonucleotides directed at exon 7 either only induced lower levels of exon skipping or no detectable skipping at all (not shown).

FIG. 5 Gel electrophoresis showing an example of low efficiency exon 6 skipping using two non-preferred antisense molecules directed at human exon 6 donor splice site. Levels of induced exon 6 skipping are either very low [H6D(+04-21)] or almost undetectable [H6D(+18-04)]. These are examples of non-preferred antisense oligonucleotides to demonstrate that antisense oligonucleotide design plays a crucial role in the efficacy of these compounds.

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FIG. 6 Gel electrophoresis showing strong and efficient human exon 6 skipping using an antisense molecules [H6A(+69+91)] directed at an exon 6 internal domain, presumably an exon splicing enhancer. This preferred compound induces consistent exon skipping at a transfection concentration of 20 nanomolar in cultured human muscle cells.

FIG. 7 Gel electrophoresis showing strong human exon 4 skipping using an antisense molecule H4A(+13+32) directed at an exon 6 internal domain, presumably an exon splicing enhancer. This preferred compound induces strong and consistent exon skipping at a transfection concentration of 20 nanomolar in cultured human muscle cells,

FIG. 8A Gel electrophoresis showing strong human exon 12 skipping using antisense molecule H12A(+52+75) directed at exon 12 internal domain.

FIG. 8B Gel electrophoresis showing strong human exon 11 skipping using antisense molecule H11A(+75+97) directed at an exon 11 internal domain.

FIG. 9A Gel electrophoresis showing strong human exon 15 skipping using antisense molecules H15A(+48+71) and H15A(-12+19) directed at an exon 15 internal domain.

FIG. 9B Gel electrophoresis showing strong human exon 16 skipping using antisense molecules H16A(-12+19) and H16A(-06+25).

FIG. 10 Gel electrophoresis showing human exon 19/20 skipping using antisense molecules H20A(+44+71) and H20A(+149+170) directed at an exon 20 and a "cocktail" of antisense oligonucleotides H19A(+35+65, H20A(+44+71) and H20A(+149+170) directed at exons 19/20.

FIG. 11 Gel electrophoresis showing human exon 19/20 skipping using "weasels" directed at exons 19 and 20.

FIG. 12 Gel electrophoresis showing exon 22 skipping using antisense molecules H22A(+125+106), H22A(+47+69), H22A(+80+101) and H22D(+13-11) directed at exon 22.

FIG. 13 Gel electrophoresis showing exon 31 skipping using antisense molecules H31D(+01-25) and H31D(+03-22); and a "cocktail" of antisense molecules directed at exon 31.

FIG. 14 Gel electrophoresis showing exon 33 skipping using antisense molecules H33A(+30+56) and H33A(+64+88) directed at exon 33.

FIG. 15 Gel electrophoresis showing exon 35 skipping using antisense molecules H35A(+141+161), H35A(+116+135), and H35A(+24+43) and a "cocktail of two antisense molecules, directed at exon 35.

FIG. 16 Gel electrophoresis showing exon 36 skipping using antisense molecules H32A(+49+73) and H36A(+26+50) directed at exon 36.

FIG. 17 Gel electrophoresis showing exon 37 skipping using antisense molecules H37A(+82+105) and H37A(+134+157) directed at exon 37.

FIG. 18 Gel electrophoresis showing exon 38 skipping using antisense molecule H38A(+88+112) directed at exon 38.

FIG. 19 Gel electrophoresis showing exon 40 skipping using antisense molecule H40A(-05+17) directed at exon 40.

FIG. 20 Gel electrophoresis showing exon 42 skipping using antisense molecule H42A(-04+23) directed at exon 42.

FIG. 21 Gel electrophoresis showing exon 46 skipping using antisense molecule H46A(+86+115) directed at exon 46.

FIG. 22 Gel electrophoresis showing exon 51, exon 52 and exon 53 skipping using various antisense molecules directed at exons 51, 52 and 53, respectively. A "cocktail" of antisense molecules is also shown directed at exon 53.

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BRIEF DESCRIPTION OF THE SEQUENCE
LISTINGS

TABLE 1A

Description of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA- like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".		
SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
1	H8A(-06+18)	GAU AGG UGG UAU CAA CAU CUG UAA
2	H8A (-03+18)	GAU AGG UGG UAU CAA CAU CUG
3	H8A(-07+18)	GAU AGG UGG UAU CAA CAU CUG UAA G
4	H8A(-06+14)	GGU GGU AUC AAC AUC UGU AA
5	H8A(-10+10)	GUA UCA ACA UCU GUA AGC AC
6	H7A(+45+67)	UGC AUG UUC CAG UCG UUG UGU GG
7	H7A(+02+26)	CAC UAU UCC AGU CAA AUA GGU CUG G
8	H7D(+15-10)	AUU UAC CAA CCU UCA GGA UCG AGU A
9	H7A(-18+03)	GGC CUA AAA CAC AUA CAC AUA
10	C6A(-10+10)	CAU UUU UGA CCU ACA UGU GG
11	C6A(-14+06)	UUU GAC CUA CAU GUG GAA AG
12	C6A(-14+12)	UAC AUU UUU GAC CUA CAU GUG GAA AG
13	C6A(-13+09)	AUU UUU GAC CUA CAU GGG AAA G
14	CH6A(+69+91)	UAC GAG UUG AUU GUC GGA CCC AG
15	C6D(+12-13)	GUG GUC UCC UUA CCU AUG ACU GUG G
16	C6D(+06-11)	GGU CUC CUU ACC UAU GA
17	H6D(+04-21)	UGU CUC AGU AAU CUU CUU ACC UAU
18	H6D(+18-04)	UCU UAC CUA UGA CUA UGG AUG AGA
19	H4A(+13+32)	GCA UGA ACU CUU GUG GAU CC
20	H4D(+04-16)	CCA GGG UAC UAC UUA CAU UA
21	H4D(-24-44)	AUC GUG UGU CAC AGC AUC CAG
22	H4A(+11+40)	UGU UCA GGG CAU GAA CUC UUG UGG AUC CUU
23	H3A(+30+60)	UAG GAG GCG CCU CCC AUC CUG UAG GUC ACU G
24	H3A(+35+65)	AGG UCU AGG AGG CGC CUC CCA UCC UGU AGG U
25	H3A(+30+54)	GCG CCU CCC AUC CUG UAG GUC ACU G
26	H3D(+46-21)	CUU CGA GGA GGU CUA GGA GGC GCC UC
27	H3A(+30+50)	CUC CCA UCC UGU AGG UCA CUG
28	H3D(+19-03)	UAC CAG UUU UUG CCC UGU CAG G
29	H3A(-06+20)	UCA AUA UGC UGC UUC CCA AAC UGA AA
30	H3A(+37+61)	CUA GGA GGC GCC UCC CAU CCU GUA G

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TABLE 1A-continued

Description of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
31	H5A(+20+50)	UUA UGA UUU CCA UCU ACG AUG UCA GUA CUU C
32	H5D(+25-05)	CUU ACC UGC CAG UGG AGG AUU AUA UUC CAA A
33	H5D(+10-15)	CAU CAG GAU UCU UAC CUG CCA GUG G
34	H5A(+10+34)	CGA UGU CAG UAC UUC CAA UAU UCA C
35	H5D(-04-21)	ACC AUU CAU CAG GAU UCU
36	H5D(+16-02)	ACC UGC CAG UGG AGG AUU
37	H5A(-07+20)	CCA AUA UUC ACU AAA UCA ACC UGU UAA
38	H5D(+18-12)	CAG GAU UGU UAC CUG CCA GUG GAG GAU UAU
39	H5A(+05+35)	ACG AUG UCA GUA CUU CCA AUA UUC ACU AAA U
40	H5A(+15+45)	AUU UCC AUC UAC GAU GUC AGU ACU UCC AAU A
41	H10A(-05+16)	CAG GAG CUU CCA AAU GCU GCA
42	H10A(-05+24)	CUU GUC UUC AGG AGC UUC CAA AUG CUG CA
43	H10A(+98+119)	UCC UCA GCA GAA AGA AGC CAC G
44	H10A(+130+149)	UUA GAA AUC UCU CCU UGU GC
45	H10A(-33-14)	UAA AUU GGG UGU UAC ACA AU
46	H11D(+26+49)	CCC UGA GGC AUU CCC AUC UUG AAU
47	H11D(+11-09)	AGG ACU UAC UUG CUU UGU UU
48	H11A(+118+140)	CUU GAA UUU AGG AGA UUC AUC UG
49	H11A(+75+97)	CAU CUU CUG AUA AUU UUC CUG UU
50	H12A(+52+75)	UCU UCU GUU UUU GUU AGC CAG UCA
51	H12A(-10+10)	UCU AUG UAA ACU GAA AAU UU
52	H12A(+11+30)	UUC UGG AGA UCC AUU AAA AC
53	H13A(+77+100)	CAG CAG UUG CGU GAU CUC CAC UAG
54	H13A(+55+75)	UUC AUC AAC UAC CAC CAC CAU
55	H13D(+06-19)	CUA AGC AAA AUA AUC UGA CCU UAA G
56	H14A(+37+64)	CUU GUA AAA GAA CCC AGC GGU CUU CUG U
57	H14A(+14+35)	CAU CUA CAG AUG UUU GCC CAU C
58	H14A(+51+73)	GAA GGA UGU CUU GUA AAA GAA CC
59	H14D(-02+18)	ACC UGU UCU UCA GUA AGA CG
60	H14D(+14-10)	CAU GAC ACA CCU GUU CUU CAG UAA
61	H14A(+61+80)	CAU UUG AGA AGG AUG UCU UG
62	H14A(-12+12)	AUC UCC CAA UAC CUG GAG AAG AGA

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TABLE 1A-continued

Description of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".		
SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
63	H15A(-12+19)	GCC AUG CAC UAA AAA GGC ACU GCA AGA CAU U
64	H15A(+48+71)	UCU UUA AAG CCA GUU GUG UGA AUC
65	H15A(+08+28)	UUU CUG AAA GCC AUG CAC UAA
66	H15D(+17-08)	GUA CAU ACG GCC AGU UUU UGA AGA C
67	H16A(-12+19)	CUA GAU CCG CUU UUA AAA CCU GUU AAA ACA A
68	H16A(-06+25)	UCU UUU CUA GAU CCG CUU UUA AAA CCU GUU A
69	H16A(-06+19)	CUA GAU CCG CUU UUA AAA CCU GUU A
70	H16A(+87+109)	CCG UCU UCU GGG UCA CUG ACU UA
71	H16A(-07+19)	CUA GAU CCG CUU UUA AAA CCU GUU AA
72	H16A(-07+13)	CCG CUU UUA AAA CCU GUU AA
73	H16A(+12+37)	UGG AUU GCU UUU UCU UUU CUA GAU CC
74	H16A(+92+116)	CAU GCU UCC GUC UUC UGG GUC ACU G
75	H16A(+45+67)	G AUC UUG UUU GAG UGA AUA CAG U
76	H16A(+105+126)	GUU AUC CAG CCA UGC UUC CGU C
77	H16D(+05-20)	UGA UAA UUG GUA UCA CUA ACC UGU G
78	H16D(+12-11)	GUA UCA CUA ACC UGU GCU GUA C
79	H19A(+35+53)	CUG CUG GCA UCU UGC AGU U
80	H19A(+35+65)	GCC UGA GCU GAU CUG CUG GCA UCU UGC AGU U
81	H20A(+44+71)	CUG GCA GAA UUC GAU CCA CCG GCU GUU C
82	H20A(+147+168)	CAG CAG UAG UUG UCA UCU GCU C
83	H20A(+185+203)	UGA UGG GGU GGU GGG UUG G
84	H20A(-08+17)	AUC UGC AUU AAC ACC CUC UAG AAA G
85	H20A(+30+53)	CCG GCU GUU CAG UUG UUC UGA GGC
86	H20A(-11+17)	AUC UGC AUU AAC ACC CUC UAG AAA GAA A
87	H20D(+08-20)	GAA GGA GAA GAG AUU CUU ACC UUA CAA A
88	H20A(+44+63)	AUU CGA UCC ACC GGC UGU UC
89	H20A(+149+168)	CAG CAG UAG UUG UCA UCU GC
90	H21A(-06+16)	GCC GGU UGA CUU CAU CCU GUG C
91	H21A(+85+106)	CUG CAU CCA GGA ACA UGG GUC C
92	H21A(+85+108)	GUC UGC AUC CAG GAA CAU GGG UC
93	H21A(+08+31)	GUU GAA GAU CUG AUA GCC GGU UGA
94	H21D(+18-07)	UAC UUA CUG UCU GUA GCU CUU UCU
95	H22A(+22+45)	CAC UCA UGG UCU CCU GAU AGC GCA

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TABLE 1A-continued

Description of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".		
SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
96	H22A(+125+106)	CUG CAA UUC CCC GAG UCU CUG C
97	H22A(+47+69)	ACU GCU GGA CCC AUG UCC UGA UG
98	H22A(+80+101)	CUA AGU UGA GGU AUG GAG AGU
99	H22D(+13-11)	UAU UCA CAG ACC UGC AAU UCC CC
100	H23A(+34+59)	ACA GUG GUG CUG AGA UAG UAU AGG CC
101	H23A(+18+39)	UAG GCC ACU UUG UUG CUC UUG C
102	H23A(+72+90)	UUC AGA GGG CGC UUU CUU C
103	H24A(+48+70)	GGG CAG GCC AUU CCU UCA GA
104	H24A(-02+22)	UCU UCA GGG UUU GUA UGU GAU UCU
105	H25A(+9+36)	CUG GGC UGA AUU GUC UGA AUA UCA CUG
106	H25A(+131+156)	CUG UUG GCA CAU GUG AUC CCA CUG AG
107	H25D(+16-08)	GUC UAU ACC UGU UGG CAC AUG UGA
108	H26A(+132+156)	UGC UUU CUG UAA UUC AUC UGG AGU U
109	H26A(-07+19)	CCU CCU UUC UGG CAU AGA CCU UCC AC
110	H26A(+68+92)	UGU GUC AUC CAU UCG UGC AUC UCU G
111	H27A(+82+106)	UUA AGG CCU CUU GUG CUA CAG GUG G
112	H27A(-4+19)	GGG GCU CUU CUU UAG CUC UCU GA
113	H27D(+19-03)	GAC UUC CAA AGU CUU GCA UUU C
114	H28A(-05+19)	GCC AAC AUG CCC AAA CUU CCU AAG
115	H28A(+99+124)	CAG AGA UUU CCU CAG CUC CGC CAG GA
116	H28D(+16-05)	CUU ACA UCU AGC ACC UCA GAG
117	H29A(+57+81)	UCC GCC AUC UGU UAG GGU CUG UGC C
118	H29A(+18+42)	AUU UGG GUU AUC CUC UGA AUG UCG C
119	H29D(+17-05)	CAU ACC UCU UCA UGU AGU UCC C
120	H30A(+122+147)	CAU UUG AGC UGC GUC CAC CUU GUC UG
121	H30A(+25+50)	UCC UGG GCA GAC UGG AUG CUC UGU UC
122	H30D(+19-04)	UUG CCU GGG CUU CCU GAG GCA UU
123	H31D(+06-18)	UUC UGA AAU AAC AUA UAC CUG UGC
124	H31D(+03-22)	UAG UUU CUG AAA UAA CAU AUA CCU G
125	H31A(+05+25)	GAC UUG UCA AAU CAG AUU GGA
126	H31D(+04-20)	GUU UCU GAA AUA ACA UAU ACC UGU
127	H32D(+04-16)	CAC CAG AAA UAC AUA CCA CA
128	H32A(+151+170)	CAA UGA UUU AGC UGU GAC UG
129	H32A(+10+32)	CGA AAC UUC AUG GAG ACA UCU UG

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TABLE 1A-continued

Description of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA- like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".		
SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
130	H32A(+49+73)	CUU GUA GAC GCU GCU CAA AAU UGG C
131	H33D(+09-11)	CAU GCA CAC ACC UUU GCU CC
132	H33A(+53+76)	UCU GUA CAA UCU GAC GUC CAG UCU
133	H33A(+30+56)	GUC UUU AUC ACC AUU UCC ACU UCA GAC
134	H33A(+64+88)	CCG UCU GCU UUU UCU GUA CAA UCU G
135	H34A(+83+104)	UCC AUA UCU GUA GCU GCC AGC C
136	H34A(+143+165)	CCA GGC AAC UUC AGA AUC CAA AU
137	H34A(-20+10)	UUU CUG UUA CCU GAA AAG AAU UAU AAU GAA
138	H34A(+46+70)	CAU UCA UUU CCU UUC GCA UCU UAC G
139	H34A(+95+120)	UGA UCU CUU UGU CAA UUC CAU AUC UG
140	H34D(+10-20)	UUC AGU GAU AUA GGU UUU ACC UUU CCC CAG
141	H34A(+72+96)	CUG UAG CUG CCA GCC AUU CUG UCA AG
142	H35A(+141+161)	UCU UCU GCU CGG GAG GUG ACA
143	H35A(+116+135)	CCA GUU ACU AUU CAG AAG AC
144	H35A(+24+43)	UCU UCA GGU GCA CCU UCU GU
145	H36A(+26+50)	UGU GAU GUG GUC CAC AUU CUG GUC A
146	H36A(-02+18)	CCA UGU GUU UCU GGU AUU CC
147	H37A(+26+50)	CGU GUA GAG UCC ACC UUU GGG CGU A
148	H37A(+82+105)	UAC UAA UUU CCU GCA GUG GUC ACC
149	H37A(+134+157)	UUC UGU GUG AAA UGG CUG CAA AUC
150	H38A(-01+19)	CCU UCA AAG GAA UGG AGG CC
151	H38A(+59+83)	UGC UGA AUU UCA GCC UCC AGU GGU U
152	H38A(+88+112)	UGA AGU CUU CCU CUU UCA GAU UCA C
153	H39A(+62+85)	CUG GCU UUC UCU CAU CUG UGA UUC
154	H39A(+39+58)	GUU GUA AGU UGU CUC CUC UU
155	H39A(+102+121)	UUG UCU GUA ACA GCU GCU GU
156	H39D(+10-10)	GCU CUA AUA CCU UGA GAG CA
157	H40A(-05+17)	CUU UGA GAC CUC AAA UCC UGU U
158	H40A(+129+153)	CUU UAU UUU CCU UUC AUC UCU GGG C
159	H42A(-04+23)	AUC GUU UCU UCA CGG ACA GUG UGC UGG
160	H42A(+86+109)	GGG CUU GUG AGA CAU GAG UGA UUU
161	H42D(+19-02)	A CCU UCA GAG GAC UCC UCU UGC
162	H43D(+10-15)	UAU GUG UUA CCU ACC CUU GUC GGU C
163	H43A(+101+120)	GGA GAG AGC UUC CUG UAG CU

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TABLE 1A-continued

Description of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA- like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".		
SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
164	H43A(+78+100)	UCA CCC UUU CCA CAG GCG UUG CA
165	H44A(+85+104)	UUU GUG UCU UUC UGA GAA AC
166	H44D(+10-10)	AAA GAC UUA CCU UAA GAU AC
167	H44A(-06+14)	AUC UGU CAA AUC GCC UGC AG
168	H46D(+16-04)	UUA CCU UGA CUU GCU CAA GC
169	H46A(+90+109)	UCC AGG UUC AAG UGG GAU AC
170	H47A(+76+100)	GCU CUU CUG GGC UUA UGG GAG CAC U
171	H47D(+25-02)	ACC UUU AUC CAC UGG AGA UUU GUC UGC
172	H47A(-9+12)	UUC CAC CAG UAA CUG AAA CAG
173	H50A(+02+30)	CCA CUC AGA GCU CAG AUC UUC UAA CUU CC
174	H50A(+07+33)	CUU CCA CUC AGA GCU CAG AUC UUC UAA
175	H50D(+07-18)	GGG AUC CAG UAU ACU UAC AGG CUC C
176	H51A(-01+25)	ACC AGA GUA ACA GUC UGA GUA GGA GC
177	H51D(+16-07)	CUC AUA CCU UCU GCU UGA UGA UC
178	H51A(+111 +134)	UUC UGU CCA AGC CCG GUU GAA AUC
179	H51A(+61+90)	ACA UCA AGG AAG AUG GCA UUU CUA GUU UGG
180	H51A(+66+90)	ACA UCA AGG AAG AUG GCA UUU CUA G
181	H51A(+66+95)	CUC CAA CAU CAA GGA AGA UGG CAU UUC UAG
182	H51D(+08-17)	AUC AUU UUU UCU CAU ACC UUC UGC U
183	H51A/D(+08-17) & (-15+)	AUC AUU UUU UCU CAU ACC UUC UGC UAG GAG CUA AAA
184	H51A(+175+195)	CAC CCA CCA UCA CCC UCU GUG
185	H51A(+199+220)	AUC AUC UCG UUG AUA UCC UCA A
186	H52A(-07+14)	UCC UGC AUU GUU GCC UGU AAG
187	H52A(+12+41)	UCC AAC UGG GGA CGC CUC UGU UCC AAA UCC
188	H52A(+17+37)	ACU GGG GAC GCC UCU GUU CCA
189	H52A(+93+112)	CCG UAA UGA UUG UUC UAG CC
190	H52D(+05-15)	UGU UAA AAA ACU UAC UUC GA
191	H53A(+45+69)	CAU UCA ACU GUU GCC UCC GGU UCU G

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TABLE 1A-continued

Description of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA- like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".		
SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
192	H53A(+39+62)	CUG UUG CCU CCG GUU CUG AAG GUG
193	H53A(+39+69)	CAU UCA ACU GUU GCC UCC GGU UCU GAA GGU G
194	H53D(+14-07)	UAC UAA CCU UGG UUU CUG UGA
195	H53A(+23+47)	CUG AAG GUG UUC UUG UAC UUC AUC C
196	H53A(+150+176)	UGU AUA GGG ACC CUC CUU CCA UGA CUC
197	H53D(+20-05)	CUA ACC UUG GUU UCU GUG AUU UUC U
198	H53D(+09-18)	GGU AUC UUU GAU ACU AAC CUU GGU UUC
199	H53A(-12+10)	AUU CUU UCA ACU AGA AUA AAA G
200	H53A(-07+18)	GAU UCU GAA UUC UUU CAA CUA GAA U
201	H53A(+07+26)	AUC CCA CUG AUU CUG AAU UC
202	H53A(+124+145)	UUG GCU CUG GCC UGU CCU AAG A
203	H46A(+86+115)	CUC UUU UCC AGG UUC AAG UGG GAU ACU AGC
204	H46A(+107+137)	CAA GCU UUU CUU UUA GUU GCU GCU CUU UUC C
205	H46A(-10+20)	UAU UCU UUU GUU CUU CUA GCC UGG AGA AAG
206	H46A(+50+77)	CUG CUU CCU CCA ACC AUA AAA CAA AUU C
207	H45A(-06+20)	CCA AUG CCA UCC UGG AGU UCC UGU AA
208	H45A(+91 +110)	UCC UGU AGA AUA CUG GCA UC
209	H45A(+125+151)	UGC AGA CCU CCU GCC ACC GCA GAU UCA
210	H45D(+16 -04)	CUA CCU CUU UUU UCU GUC UG
211	H45A(+71+90)	UGU UUU UGA GGA UUG CUG AA

TABLE 1B

Description of a cocktail of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA.		
SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
81	H20A(+44+71)	CUG GCA GAA UUC GAU CCA CCG GCU
82	H20A(+147+168)	GUU C CAG CAG UAG UUG UCA UCU GCU C
80	H19A(+35+65)	GCC UGA GCU GAU CUG CUG GCA UCU
81	H20A(+44+71)	UGC
82	H20A(+147+168)	AGU U CUG GCA GAA UUC GAU CCA CCG GCU GUU C CAG CAG UAG UUG UCA UCU GCU C

TABLE 1B-continued

Description of a cocktail of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA.		
SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
194	H53D(+14-07)	UAC UAA CCU UGG UUU CUG UGA
195	H53A(+23+47)	CUG AAG GUG UUC UUG UAC UUC AUC C
196	H53A(+150+175)	UGU AUA GGG ACC CUC CUU CCA UGA CUC

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TABLE 1C

Description of a "weasel" of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA.		
SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
81	H20A(+44+71) -	CUG GCA GAA UUC GAU CCA CCG GCU GUU C-
82	H20A(+147+168)	CAG CAG UAG UUG UCA UCU GCU C
80	H19A(+35+65) -	GCC UGA GCU GAU CUG CUG GCA UCU UGC
		AGU U
88	H20A(+44+63) -	-AUU CGA UCC ACC GGC UGU UC-
79	H20A(+149+168)	CUG CUG GCA UCU UGC AGU U
80	H19A(+35+65) -	GCC UGA GCU GAU CUG CUG GCA UCU UGC
		AGU U
88	H20A(+44+63)	-AUU CGA UCC ACC GGC UGU UC-
80	H19A(+35+65) -	GCC UGA GCU GAU CUG CUG GCA UCU UGC
		AGU U
79	H20A(+149+168)	-CUG CUG GCA UCU UGC AGU U
138	H34A(+46+70) -	CAU UCA UUU CCU UUC GCA UCU UAC G-
139	H34A(+94+120)	UGA UCU CUU UGU CAA UUC CAU AUC UG
124	H31D(+03-22) -	UAG UUU CUG AAA UAA CAU AUA CCU G-
	UU-	UU-
144	H35A(+24+43)	UCU UCA GGU GCA CCU UCU GU
195	H53A(+23+47) -	CUG AAG GUG UUC UUG UAC UUC AUC C-
	AA-	
196	H53A(+150+175) -	UGU AUA GGG ACC CUC CUU CCA UGA CUC-
	AA-	
194	H53D(+14-07)	UAC UAA CCU UGG UUU CUG UGA
-	Aimed at exons	CAG CAG UAG UUG UCA UCU GCU CAA CUG
212	19/20/20	GCA GAA UUC GAU CCA CCG GCU GUU CAA
		GCC UGA GCU GAU CUG CUC GCA UCU
		UGC AGU

DETAILED DESCRIPTION OF THE INVENTION

General

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variation and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in the specification, individually or collectively and any and all combinations or any two or more of the steps or features.

The present invention is not to be limited in scope by the specific embodiments described herein, which are intended for the purpose of exemplification only. Functionally equivalent products, compositions and methods are clearly within the scope of the invention as described herein.

Sequence identity numbers (SEQ ID NO:) containing nucleotide and amino acid sequence information included in this specification are collected at the end of the description and have been prepared using the programme PatentIn Version 3.0. Each nucleotide or amino acid sequence is identified in the sequence listing by the numeric indicator <210> followed by the sequence identifier (e.g. <210>1, <210>2, etc.). The length, type of sequence and source organism for each nucleotide or amino acid sequence are indicated by information provided in the numeric indicator fields <211>, <212> and <213>, respectively. Nucleotide and amino acid sequences referred to in the specification are

defined by the information provided in numeric indicator field <400> followed by the sequence identifier (e.g. <400>1, <400>2, etc.).

An antisense molecules nomenclature system was proposed and published to distinguish between the different antisense molecules (see Mann et al., (2002) *J Gen Med* 4, 644-654). This nomenclature became especially relevant when testing several slightly different antisense molecules, all directed at the same target region, as shown below:

H#A/D(x,y).

The first letter designates the species (e.g. H: human, M: murine, C: canine) "#" designates target dystrophin exon number.

"A/D" indicates acceptor or donor splice site at the beginning and end of the exon, respectively.

(x y) represents the annealing coordinates where "-" or "+" indicate intronic or exonic sequences respectively. As an example, A(-6+18) would indicate the last 6 bases of the intron preceding the target exon and the first 18 bases of the target exon. The closest splice site would be the acceptor so these coordinates would be preceded with an "A". Describing annealing coordinates at the donor splice site could be D(+2-18) where the last 2 exonic bases and the first 18 intronic bases correspond to the annealing site of the antisense molecule. Entirely exonic annealing coordinates that would be represented by A(+65+85), that is the site between the 65th and 85th nucleotide from the start of that exon.

The entire disclosures of all publications (including patents, patent applications, journal articles, laboratory manu-

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als, books, or other documents) cited herein are hereby incorporated by reference. No admission is made that any of the references constitute prior art or are part of the common general knowledge of those working in the field to which this invention relates.

As used necessarily herein the term "derived" and "derived from" shall be taken to indicate that a specific integer may be obtained from a particular source albeit not directly from that source.

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

Other definitions for selected terms used herein may be found within the detailed description of the invention and apply throughout. Unless otherwise defined, all other scientific and technical terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which the invention belongs.

Description of the Preferred Embodiment

When antisense molecule(s) are targeted to nucleotide sequences involved in splicing in exons within pre-mRNA sequences, normal splicing of the exon may be inhibited causing the splicing machinery to by-pass the entire mutated exon from the mature mRNA. The concept of antisense oligonucleotide induced exon skipping is shown in FIG. 2. In many genes, deletion of an entire exon would lead to the production of a non-functional protein through the loss of important functional domains or the disruption of the reading frame. In some proteins, however, it is possible to shorten the protein by deleting one or more exons, without disrupting the reading frame, from within the protein without seriously altering the biological activity of the protein. Typically, such proteins have a structural role and/or possess functional domains at their ends. The present invention describes antisense molecules capable of binding to specified dystrophin pre-mRNA targets and re-directing processing of that gene.

Antisense Molecules

According to a first aspect of the invention, there is provided antisense molecules capable of binding to a selected target to induce exon skipping. To induce exon skipping in exons of the Dystrophin gene transcript, the antisense molecules are preferably selected from the group of compounds shown in Table 1A. There is also provided a combination or "cocktail" of two or more antisense oligonucleotides capable of binding to a selected target to induce exon skipping. To induce exon skipping in exons of the Dystrophin gene transcript, the antisense molecules in a "cocktail" are preferably selected from the group of compounds shown in Table 1B. Alternatively, exon skipping may be induced by antisense oligonucleotides joined together "weasels" preferably selected from the group of compounds shown in Table 1C.

Designing antisense molecules to completely mask consensus splice sites may not necessarily generate any skipping of the targeted exon. Furthermore, the inventors have discovered that size or length of the antisense oligonucleotide itself is not always a primary factor when designing antisense molecules. With some targets such as exon 19, antisense oligonucleotides as short as 12 bases were able to induce exon skipping, albeit not as efficiently as longer (20-31 bases) oligonucleotides. In some other targets, such as murine dystrophin exon 23, antisense oligonucleotides

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only 17 residues long were able to induce more efficient skipping than another overlapping compound of 25 nucleotides.

The inventors have also discovered that there does not appear to be any standard motif that can be blocked or masked by antisense molecules to redirect splicing. In some exons, such as mouse dystrophin exon 23, the donor splice site was the most amenable to target to re-direct skipping of that exon. It should be noted that designing and testing a series of exon 23 specific antisense molecules to anneal to overlapping regions of the donor splice site showed considerable variation in the efficacy of induced exon skipping. As reported in Mann et al., (2002) there was a significant variation in the efficiency of bypassing the nonsense mutation depending upon antisense oligonucleotide annealing ("Improved antisense oligonucleotide induced exon skipping in the mdx mouse model of muscular dystrophy". *J Gen Med* 4: 644-654). Targeting the acceptor site of exon 23 or several internal domains was not found to induce any consistent exon 23 skipping.

In other exons targeted for removal, masking the donor splice site did not induce any exon skipping. However, by directing antisense molecules to the acceptor splice site (human exon 8 as discussed below), strong and sustained exon skipping was induced. It should be noted that removal of human exon 8 was tightly linked with the co-removal of exon 9. There is no strong sequence homology between the exon 8 antisense oligonucleotides and corresponding regions of exon 9 so it does not appear to be a matter of cross reaction. Rather the splicing of these two exons is inextricably linked. This is not an isolated instance as the same effect is observed in canine cells where targeting exon 8 for removal also resulted in the skipping of exon 9. Targeting exon 23 for removal in the mouse dystrophin pre-mRNA also results in the frequent removal of exon 22 as well. This effect occurs in a dose dependent manner and also indicates close coordinated processing of 2 adjacent exons.

In other targeted exons, antisense molecules directed at the donor or acceptor splice sites did not induce exon skipping while annealing antisense molecules to intra-exonic regions (i.e. exon splicing enhancers within human dystrophin exon 6) was most efficient at inducing exon skipping. Some exons, both mouse and human exon 19 for example, are readily skipped by targeting antisense molecules to a variety of motifs. That is, targeted exon skipping is induced after using antisense oligonucleotides to mask donor and acceptor splice sites or exon splicing enhancers.

To identify and select antisense oligonucleotides suitable for use in the modulation of exon skipping, a nucleic acid sequence whose function is to be modulated must first be identified. This may be, for example, a gene (or mRNA transcribed from the gene) whose expression is associated with a particular disorder or disease state, or a nucleic acid molecule from an infectious agent. Within the context of the present invention, preferred target site(s) are those involved in mRNA splicing (i.e. splice donor sites, splice acceptor sites, or exonic splicing enhancer elements). Splicing branch points and exon recognition sequences or splice enhancers are also potential target sites for modulation of mRNA splicing.

Preferably, the present invention aims to provide antisense molecules capable of binding to a selected target in the dystrophin pre-mRNA to induce efficient and consistent exon skipping. Duchenne muscular dystrophy arises from mutations that preclude the synthesis of a functional dystrophin gene product. These Duchenne muscular dystrophy gene defects are typically nonsense mutations or genomic

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rearrangements such as deletions, duplications or micro-deletions or insertions that disrupt the reading frame. As the human dystrophin gene is a large and complex gene with the 79 exons being spliced together to generate a mature mRNA with an open reading frame of approximately 11,000 bases, there are many positions where these mutations can occur. Consequently, a comprehensive antisense oligonucleotide based therapy to address many of the different disease-causing mutations in the dystrophin gene will require that many exons can be targeted for removal during the splicing process.

Within the context of the present invention, preferred target site(s) are those involved in mRNA splicing (i.e. splice donor sites, splice acceptor sites or exonic splicing enhancer elements). Splicing branch points and exon recognition sequences or splice enhancers are also potential target sites for modulation of mRNA splicing.

The oligonucleotide and the DNA or RNA are complementary to each other when a sufficient number of corresponding positions in each molecule are occupied by nucleotides which can hydrogen bond with each other. Thus, "specifically hybridisable" and "complementary" are terms which are used to indicate a sufficient degree of complementarity or precise pairing such that stable and specific binding occurs between the oligonucleotide and the DNA or RNA target. It is understood in the art that the sequence of an antisense molecule need not be 100% complementary to that of its target sequence to be specifically hybridisable. An antisense molecule is specifically hybridisable when binding of the compound to the target DNA or RNA molecule interferes with the normal function of the target DNA or RNA to cause a loss of utility, and there is a sufficient degree of complementarity to avoid non-specific binding of the antisense compound to non-target sequences under conditions in which specific binding is desired, i.e., under physiological conditions in the case of in vivo assays or therapeutic treatment, and in the case of in vitro assays, under conditions in which the assays are performed.

While the above method may be used to select antisense molecules capable of deleting any exon from within a protein that is capable of being shortened without affecting its biological function, the exon deletion should not lead to a reading frame shift in the shortened transcribed mRNA. Thus, if in a linear sequence of three exons the end of the first exon encodes two of three nucleotides in a codon and the next exon is deleted then the third exon in the linear sequence must start with a single nucleotide that is capable of completing the nucleotide triplet for a codon. If the third exon does not commence with a single nucleotide there will be a reading frame shift that would lead to the generation of truncated or a non-functional protein.

It will be appreciated that the codon arrangements at the end of exons in structural proteins may not always break at the end of a codon, consequently there may be a need to delete more than one exon from the pre-mRNA to ensure in-frame reading of the mRNA. In such circumstances, a plurality of antisense oligonucleotides may need to be selected by the method of the invention wherein each is directed to a different region responsible for inducing splicing in the exons that are to be deleted.

The length of an antisense molecule may vary so long as it is capable of binding selectively to the intended location within the pre-mRNA molecule. The length of such sequences can be determined in accordance with selection procedures described herein. Generally, the antisense molecule will be from about 10 nucleotides in length up to about 50 nucleotides in length. It will be appreciated however that

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any length of nucleotides within this range may be used in the method. Preferably, the length of the antisense molecule is between 17 to 30 nucleotides in length.

In order to determine which exons can be connected in a dystrophin gene, reference should be made to an exon boundary map. Connection of one exon with another is based on the exons possessing the same number at the 3' border as is present at the 5' border of the exon to which it is being connected. Therefore, if exon 7 were deleted, exon 6 must connect to either exons 12 or 18 to maintain the reading frame. Thus, antisense oligonucleotides would need to be selected which redirected splicing for exons 7 to 11 in the first instance or exons 7 to 17 in the second instance. Another and somewhat simpler approach to restore the reading frame around an exon 7 deletion would be to remove the two flanking exons. Induction of exons 6 and 8 skipping should result in an in-frame transcript with the splicing of exons 5 to 9. In practise however, targeting exon 8 for removal from the pre-mRNA results in the co-removal of exon 9 so the resultant transcript would have exon 5 joined to exon 10. The inclusion or exclusion of exon 9 does not alter the reading frame. Once the antisense molecules to be tested have been identified, they are prepared according to standard techniques known in the art. The most common method for producing antisense molecules is the methylation of the 2' hydroxyribose position and the incorporation of a phosphorothioate backbone produces molecules that superficially resemble RNA but that are much more resistant to nuclease degradation.

To avoid degradation of pre-mRNA during duplex formation with the antisense molecules, the antisense molecules used in the method may be adapted to minimise or prevent cleavage by endogenous RNase H. This property is highly preferred as the treatment of the RNA with the unmethylated oligonucleotides either intracellularly or in crude extracts that contain RNase H leads to degradation of the pre-mRNA: antisense oligonucleotide duplexes. Any form of modified antisense molecules that is capable of bypassing or not inducing such degradation may be used in the present method. An example of antisense molecules which when duplexed with RNA are not cleaved by cellular RNase H is 2'-O-methyl derivatives. 2'-O-methyl-oligoribonucleotides are very stable in a cellular environment and in animal tissues, and their duplexes with RNA have higher T_m values than their ribo- or deoxyribo-counterparts.

Antisense molecules that do not activate RNase H can be made in accordance with known techniques (see, e.g., U.S. Pat. No. 5,149,797). Such antisense molecules, which may be deoxyribonucleotide or ribonucleotide sequences, simply contain any structural modification which sterically hinders or prevents binding of RNase H to a duplex molecule containing the oligonucleotide as one member thereof, which structural modification does not substantially hinder or disrupt duplex formation. Because the portions of the oligonucleotide involved in duplex formation are substantially different from those portions involved in RNase H binding thereto, numerous antisense molecules that do not activate RNase H are available. For example, such antisense molecules may be oligonucleotides wherein at least one, or all, of the inter-nucleotide bridging phosphate residues are modified phosphates, such as methyl phosphonates, methyl phosphorothioates, phosphoromorpholidates, phosphoropiperazides and phosphoramidates. For example, every other one of the internucleotide bridging phosphate residues may be modified as described. In another non-limiting example, such antisense molecules are molecules wherein at least one, or all, of the nucleotides contain a 2' lower alkyl

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moiety (e.g., C₁-C₄, linear or branched, saturated or unsaturated alkyl, such as methyl, ethyl, ethenyl, propyl, 1-propenyl, 2-propenyl, and isopropyl). For example, every other one of the nucleotides may be modified as described.

While antisense oligonucleotides are a preferred form of the antisense molecules, the present invention comprehends other oligomeric antisense molecules, including but not limited to oligonucleotide mimetics such as are described below.

Specific examples of preferred antisense compounds useful in this invention include oligonucleotides containing modified backbones or non-natural inter-nucleoside linkages. As defined in this specification, oligonucleotides having modified backbones include those that retain a phosphorus atom in the backbone and those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified oligonucleotides that do not have a phosphorus atom in their inter-nucleoside backbone can also be considered to be oligonucleosides.

In other preferred oligonucleotide mimetics, both the sugar and the inter-nucleoside linkage, i.e., the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, an oligonucleotide mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar backbone of an oligonucleotide is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone.

Modified oligonucleotides may also contain one or more substituted sugar moieties. Oligonucleotides may also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. Certain nucleobases are particularly useful for increasing the binding affinity of the oligomeric compounds of the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2° C. and are presently preferred base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

Another modification of the oligonucleotides of the invention involves chemically linking to the oligonucleotide one or more moieties or conjugates that enhance the activity, cellular distribution or cellular uptake of the oligonucleotide. Such moieties include but are not limited to lipid moieties such as a cholesterol moiety, cholic acid, a thioether, e.g., hexyl-S-tritylthiol, a thiocholesterol, an aliphatic chain, e.g., dodecandiol or undecyl residues, a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate, a polyamine or a polyethylene glycol chain, or adamantane acetic acid, a palmityl moiety, or an octadecylamine or hexylamino-carbonyl-oxcholesterol moiety.

It is not necessary for all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications may be incorporated in a single compound or even at a single nucleoside within an oligonucleotide. The present invention also includes antisense compounds that are chimeric compounds. "Chimeric" antisense compounds or "chimeras," in the context of this invention, are antisense molecules, particularly oligonucle-

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otides, which contain two or more chemically distinct regions, each made up of at least one monomer unit, i.e., a nucleotide in the case of an oligonucleotide compound. These oligonucleotides typically contain at least one region wherein the oligonucleotide is modified so as to confer upon the increased resistance to nuclease degradation, increased cellular uptake, and an additional region for increased binding affinity for the target nucleic acid.

Methods of Manufacturing Antisense Molecules

The antisense molecules used in accordance with this invention may be conveniently and routinely made through the well-known technique of solid phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems (Foster City, Calif.). One method for synthesizing oligonucleotides on a modified solid support is described in U.S. Pat. No. 4,458,066.

Any other means for such synthesis known in the art may additionally or alternatively be employed. It is well known to use similar techniques to prepare oligonucleotides such as the phosphorothioates and alkylated derivatives. In one such automated embodiment, diethyl-phosphoramidites are used as starting materials and may be synthesized as described by Beaucage, et al., (1981) *Tetrahedron Letters*, 22:1859-1862.

The antisense molecules of the invention are synthesized in vitro and do not include antisense compositions of biological origin, or genetic vector constructs designed to direct the in vivo synthesis of antisense molecules. The molecules of the invention may also be mixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures or mixtures of compounds, as for example, liposomes, receptor targeted molecules, oral, rectal, topical or other formulations, for assisting in uptake, distribution and/or absorption.

Therapeutic Agents

The present invention also can be used as a prophylactic or therapeutic, which may be utilized for the purpose of treatment of a genetic disease.

Accordingly, in one embodiment the present invention provides antisense molecules that bind to a selected target in the dystrophin pre-mRNA to induce efficient and consistent exon skipping described herein in a therapeutically effective amount admixed with a pharmaceutically acceptable carrier, diluent, or excipient.

The phrase "pharmaceutically acceptable" refers to molecular entities and compositions that are physiologically tolerable and do not typically produce an allergic or similarly untoward reaction, such as gastric upset and the like, when administered to a patient. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water or saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Suitable pharmaceutical carriers are described in Martin, *Remington's Pharmaceutical Sciences*, 18th Ed., Mack Publishing Co., Easton, Pa., (1990).

In a more specific form of the invention there are provided pharmaceutical compositions comprising therapeutically effective amounts of an antisense molecule together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions include diluents of various buffer content (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength and additives such as detergents and solubilizing agents (e.g.,

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Tween 80, Polysorbate 80), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimerosal, benzyl alcohol) and bulking substances (e.g., lactose, mannitol). The material may be incorporated into particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc. or into liposomes. Hylauronic acid may also be used. Such compositions may influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the present proteins and derivatives. See, e.g., Martin, *Remington's Pharmaceutical Sciences*, 18th Ed. (1990, Mack Publishing Co., Easton, Pa. 18042) pages 1435-1712 that are herein incorporated by reference. The compositions may be prepared in liquid form, or may be in dried powder, such as lyophilised form.

It will be appreciated that pharmaceutical compositions provided according to the present invention may be administered by any means known in the art. Preferably, the pharmaceutical compositions for administration are administered by injection, orally, or by the pulmonary, or nasal route. The antisense molecules are more preferably delivered by intravenous, intra-arterial, intraperitoneal, intramuscular, or subcutaneous routes of administration.

Antisense Molecule Based Therapy

Also addressed by the present invention is the use of antisense molecules of the present invention, for manufacture of a medicament for modulation of a genetic disease.

The delivery of a therapeutically useful amount of antisense molecules may be achieved by methods previously published. For example, intracellular delivery of the antisense molecule may be via a composition comprising an admixture of the antisense molecule and an effective amount of a block copolymer. An example of this method is described in US patent application US 20040248833.

Other methods of delivery of antisense molecules to the nucleus are described in Mann C J et al., (2001) [*"Antisense-induced exon skipping and the synthesis of dystrophin in the mdx mouse"*]. *Proc., Natl. Acad. Science*, 98(1) 42-47J and in Gebiski et al., (2003). *Human Molecular Genetics*, 12(15): 1801-1811.

A method for introducing a nucleic acid molecule into a cell by way of an expression vector either as naked DNA or complexed to lipid carriers, is described in U.S. Pat. No. 6,806,084.

It may be desirable to deliver the antisense molecule in a colloidal dispersion system. Colloidal dispersion systems include macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes or liposome formulations.

Liposomes are artificial membrane vesicles which are useful as delivery vehicles in vitro and in vivo. These formulations may have net cationic, anionic or neutral charge characteristics and are useful characteristics with in vitro, in vivo and ex vivo delivery methods. It has been shown that large unilamellar vesicles (LUV), which range in size from 0.2-4.0 μ m can encapsulate a substantial percentage of an aqueous buffer containing large macromolecules. RNA, and DNA can be encapsulated within the aqueous interior and be delivered to cells in a biologically active form (Fraley, et al., *Trends Biochem. Sci.*, 6:77, 1981).

In order for a liposome to be an efficient gene transfer vehicle, the following characteristics should be present: (1) encapsulation of the antisense molecule of interest at high efficiency while not compromising their biological activity; (2) preferential and substantial binding to a target cell in comparison to non-target cells; (3) delivery of the aqueous

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contents of the vesicle to the target cell cytoplasm at high efficiency; and (4) accurate and effective expression of genetic information (Mannino, et al., *Biotechniques*, 6:682, 1988).

The composition of the liposome is usually a combination of phospholipids, particularly high-phase-transition-temperature phospholipids, usually in combination with steroids, especially cholesterol. Other phospholipids or other lipids may also be used. The physical characteristics of liposomes depend on pH, ionic strength, and the presence of divalent cations.

Alternatively, the antisense construct may be combined with other pharmaceutically acceptable carriers or diluents to produce a pharmaceutical composition. Suitable carriers and diluents include isotonic saline solutions, for example phosphate-buffered saline. The composition may be formulated for parenteral, intramuscular, intravenous, subcutaneous, intraocular, oral or transdermal administration.

The routes of administration described are intended only as a guide since a skilled practitioner will be able to determine readily the optimum route of administration and any dosage for any particular animal and condition. Multiple approaches for introducing functional new genetic material into cells, both in vitro and in vivo have been attempted (Friedmann (1989) *Science*, 244:1275-1280).

These approaches include integration of the gene to be expressed into modified retroviruses (Friedmann (1989) supra; Rosenberg (1991) *Cancer Research* 51(18), suppl.: 5074S-5079S); integration into non-retrovirus vectors (Rosenfeld, et al. (1992) *Cell*, 68:143-155; Rosenfeld, et al. (1991) *Science*, 252:431-434); or delivery of a transgene linked to a heterologous promoter-enhancer element via liposomes (Friedmann (1989), supra; Brigham, et al. (1989) *Am. J. Med. Sci.*, 298:278-281; Nabel, et al. (1990) *Science*, 249:1285-1288; Hazinski, et al. (1991) *Am. J. Resp. Cell Molec. Biol.*, 4:206-209; and Wang and Huang (1987) *Proc. Natl. Acad. Sci. (USA)*, 84:7851-7855); coupled to ligand-specific, cation-based transport systems (Wu and Wu (1988) *J. Biol. Chem.*, 263:14621-14624) or the use of naked DNA, expression vectors (Nabel et al. (1990), supra; Wolff et al. (1990) *Science*, 247:1465-1468). Direct injection of transgenes into tissue produces only localized expression (Rosenfeld (1992) supra; Rosenfeld et al. (1991) supra; Brigham et al. (1989) supra; Nabel (1990) supra; and Hazinski et al. (1991) supra). The Brigham et al. group (*Am. J. Med. Sci.* (1989) 298:278-281 and *Clinical Research* (1991) 39 (abstract)) have reported in vivo transfection only of lungs of mice following either intravenous or intratracheal administration of a DNA liposome complex. An example of a review article of human gene therapy procedures is: Anderson, *Science* (1992) 256:808-813.

The antisense molecules of the invention encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which, upon administration to an animal including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to prodrugs and pharmaceutically acceptable salts of the compounds of the invention, pharmaceutically acceptable salts of such pro-drugs, and other bioequivalents.

The term "pharmaceutically acceptable salts" refers to physiologically and pharmaceutically acceptable salts of the compounds of the invention: i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto.

For oligonucleotides, preferred examples of pharmaceutically acceptable salts include but are not limited to (a) salts

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formed with cations such as sodium, potassium, ammonium, magnesium, calcium, polyamines such as spermine and spermidine, etc.; (b) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; (c) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, malefic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalene-disulfonic acid, polygalacturonic acid, and the like; and (d) salts formed from elemental anions such as chlorine, bromine, and iodine. The pharmaceutical compositions of the present invention may be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic and to mucous membranes including rectal delivery), pulmonary, e.g., by inhalation or insufflation of powders or aerosols, (including by nebulizer, intratracheal, intranasal, epidermal and transdermal), oral or parenteral. Parenteral administration includes intravenous, intra-arterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Oligonucleotides with at least one 2'-O-methoxyethyl modification are believed to be particularly useful for oral administration.

The pharmaceutical formulations of the present invention, which may conveniently be presented in unit dosage form, may be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Kits of the Invention

The invention also provides kits for treatment of a patient with a genetic disease which kit comprises at least an antisense molecule, packaged in a suitable container, together with instructions for its use.

In a preferred embodiment, the kits will contain at least one antisense molecule as shown in Table 1A, or a cocktail of antisense molecules as shown in Table 1B or a "weasel" compound as shown in Table 1C. The kits may also contain peripheral reagents such as buffers, stabilizers, etc.

Those of ordinary skill in the field should appreciate that applications of the above method has wide application for identifying antisense molecules suitable for use in the treatment of many other diseases.

EXAMPLES

The following Examples serve to more fully describe the manner of using the above-described invention, as well as to set forth the best modes contemplated for carrying out various aspects of the invention. It is understood that these Examples in no way serve to limit the true scope of this invention, but rather are presented for illustrative purposes. The references cited herein are expressly incorporated by reference.

Methods of molecular cloning, immunology and protein chemistry, which are not explicitly described in the following examples, are reported in the literature and are known by those skilled in the art. General texts that described conventional molecular biology, microbiology, and recombinant

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DNA techniques within the skill of the art, included, for example: Sambrook et al, *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989); Glover ed., *DNA Cloning: A Practical Approach*, Volumes I and II, MRL Press, Ltd., Oxford, U. K. (1985); and Ausubel, F., Brent, R., Kingston, R. E., Moore, D. D., Seidman, J. G., Smith, J. A., Struhl, K. *Current Protocols in Molecular Biology*. Greene Publishing Associates/Wiley Intersciences, New York (2002).

Determining Induced Exon Skipping in Human Muscle Cells

Attempts by the inventors to develop a rational approach in antisense molecules design were not completely successful as there did not appear to be a consistent trend that could be applied to all exons. As such, the identification of the most effective and therefore most therapeutic antisense molecules compounds has been the result of empirical studies.

These empirical studies involved the use of computer programs to identify motifs potentially involved in the splicing process. Other computer programs were also used to identify regions of the pre-mRNA which may not have had extensive secondary structure and therefore potential sites for annealing of antisense molecules. Neither of these approaches proved completely reliable in designing antisense oligonucleotides for reliable and efficient induction of exon skipping.

Annealing sites on the human dystrophin pre-mRNA were selected for examination, initially based upon known or predicted motifs or regions involved in splicing. 2OMe antisense oligonucleotides were designed to be complementary to the target sequences under investigation and were synthesised on an Expedite 8909 Nucleic Acid Synthesiser. Upon completion of synthesis, the oligonucleotides were cleaved from the support column and de-protected in ammonium hydroxide before being desalted. The quality of the oligonucleotide synthesis was monitored by the intensity of the trityl signals upon each deprotection step during the synthesis as detected in the synthesis log. The concentration of the antisense oligonucleotide was estimated by measuring the absorbance of a diluted aliquot at 260 nm.

Specified amounts of the antisense molecules were then tested for their ability to induce exon skipping in an in vitro assay, as described below.

Briefly, normal primary myoblast cultures were prepared from human muscle biopsies obtained after informed consent. The cells were propagated and allowed to differentiate into myotubes using standard culturing techniques. The cells were then transfected with the antisense oligonucleotides by delivery of the oligonucleotides to the cells as cationic lipoplexes, mixtures of antisense molecules or cationic liposome preparations.

The cells were then allowed to grow for another 24 hours, after which total RNA was extracted and molecular analysis commenced. Reverse transcriptase amplification (RT-PCR) was undertaken to study the targeted regions of the dystrophin pre-mRNA or induced exonic re-arrangements.

For example, in the testing of an antisense molecule for inducing exon 19 skipping the RT-PCR test scanned several exons to detect involvement of any adjacent exons. For example, when inducing skipping of exon 19, RT-PCR was carried out with primers that amplified across exons 17 and 21. Amplifications of even larger products in this area (i.e. exons 13-26) were also carried out to ensure that there was

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minimal amplification bias for the shorter induced skipped transcript. Shorter or exon skipped products tend to be amplified more efficiently and may bias the estimated of the normal and induced transcript.

The sizes of the amplification reaction products were estimated on an agarose gel and compared against appropriate size standards. The final confirmation of identity of these products was carried out by direct DNA sequencing to establish that the correct or expected exon junctions have been maintained.

Once efficient exon skipping had been induced with one antisense molecule, subsequent overlapping antisense molecules may be synthesized and then evaluated in the assay as described above. Our definition of an efficient antisense molecule is one that induces strong and sustained exon skipping at transfection concentrations in the order of 300 nM or less.

Antisense Oligonucleotides Directed at Exon 8

Antisense oligonucleotides directed at exon 8 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

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efficient antisense molecules only induced exon skipping at concentrations of 300 nM and above. Therefore, we have shown that targeting of the antisense molecules to motifs involved in the splicing process plays a crucial role in the overall efficacy of that compound.

Efficacy refers to the ability to induce consistent skipping of a target exon. However, sometimes skipping of the target exons is consistently associated with a flanking exon. That is, we have found that the splicing of some exons is tightly linked. For example, in targeting exon 23 in the mouse model of muscular dystrophy with antisense molecules directed at the donor site of that exon, dystrophin transcripts missing exons 22 and 23 are frequently detected. As another example, when using an antisense molecule directed to exon 8 of the human dystrophin gene, all induced transcripts are missing both exons 8 and 9. Dystrophin transcripts missing only exon 8 are not observed.

Table 2 below discloses antisense molecule sequences that induce exon 8 (and 9) skipping.

TABLE 2

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
1	H8A(-06+18)	5'-GAU AGG UGG UAU CAA CAU CUG UAA	Very strong to 20 nM
2	H8A (-03+18)	5'-GAU AGG UGG UAU CAA CAU CUG	Very strong skipping to 40 nM
3	H8A(-07+18)	5'-GAU AGG UGG UAU CAA CAU CUG UAA G	Strong skipping to 40 nM
4	H8A(-06+14)	5'-GGU GGU AUC AAC AUC UGU AA	Skipping to 300 nM
5	H8A(-10+10)	5'-GUA UCA ACA UCU GUA AGC AC	Patchy/weak skipping to 100 nM

FIG. 3 shows differing efficiencies of two antisense molecules directed at exon 8 acceptor splice site. H8A(-06+18) [SEQ ID NO:1], which anneals to the last 6 bases of intron 7 and the first 18 bases of exon 8, induces substantial exon 8 and 9 skipping when delivered into cells at a concentration of 20 nM. The shorter antisense molecule, H8A(-06+14) [SEQ ID NO: 4] was only able to induce exon 8 and 9 skipping at 300 nM, a concentration some 15 fold higher than H8A(-06+18), which is the preferred antisense molecule.

This data shows that some particular antisense molecules induce efficient exon skipping while another antisense molecule, which targets a near-by or overlapping region, can be much less efficient. Titration studies show one compound is able to induce targeted exon skipping at 20 nM while the less

Antisense Oligonucleotides Directed at Exon 7

Antisense oligonucleotides directed at exon 7 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 4 shows the preferred antisense molecule, H7A(+45+67) [SEQ ID NO: 6], and another antisense molecule, H7A(+2+26) [SEQ ID NO: 7], inducing exon 7 skipping. Nested amplification products span exons 3 to 9. Additional products above the induced transcript missing exon 7 arise from amplification from carry-over outer primers from the RT-PCR as well as heteroduplex formation.

Table 3 below discloses antisense molecule sequences for induced exon 7 skipping.

TABLE 3

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
6	H7A(+45+67)	5'-UGC AUG UUC CAG UCG UUG UGU GG	Strong skipping to 20 nM

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TABLE 3-continued

Antisense SEQ ID name	Sequence	Ability to induce skipping
7 H7A(+02+26)	5'-CAC UAU UCC AGU CAA AUA GGU CUG G	Weak skipping at 100 nM
8 H7D(+15-10)	5'-AUU UAC CAA CCU UCA GGA UCG AGU A	Weak skipping to 300 nM
9 H7A(-18+03)	5'-GGC CUA AAA CAC AUA CAC AUA	Weak skipping to 300 nM

Antisense Oligonucleotides Directed at Exon 6

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Antisense oligonucleotides directed at exon 6 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 5 shows an example of two non-preferred antisense molecules inducing very low levels of exon 6 skipping in cultured human cells. Targeting this exon for specific removal was first undertaken during a study of the canine model using the oligonucleotides as listed in Table 4, below. Some of the human specific oligonucleotides were also evaluated, as shown in FIG. 5. In this example, both antisense molecules target the donor splice site and only induced low levels of exon 6 skipping. Both H6D(+4-21) [SEQ ID NO: 17] and H6D(+18-4) [SEQ ID NO: 18] would be regarded as non-preferred antisense molecules.

One antisense oligonucleotide that induced very efficient exon 6 skipping in the canine model, C6A(+69+91) [SEQ ID NO: 14], would anneal perfectly to the corresponding region in human dystrophin exon 6. This compound was evaluated, found to be highly efficient at inducing skipping of that target exon, as shown in FIG. 6 and is regarded as the preferred compound for induced exon 6 skipping. Table 4 below discloses antisense molecule sequences for induced exon 6 skipping.

TABLE 4

Antisense Oligo SEQ ID name	Sequence	Ability to induce skipping
10 C6A(-10+10)	5' CAU UUU UGA CCU ACA UGU GG	No skipping
11 C6A(-14+06)	5' UUU GAC CUA CAU GUG GAA AG	No skipping
12 C6A(-14+12)	5' UAC AUU UUU GAC CUA CAU GUG GAA AG	No skipping
13 C6A(-13+09)	5' AUU UUU GAC CUA CAU GGG AAA G	No skipping
14 CH6A(+69+91)	5' UAC GAG UUG AUU GUC GGA CCC AG	Strong skipping to 20 nM
15 C6D(+12-13)	5' GUG GUC UCC UUA CCU AUG ACU GUG G	Weak skipping at 300 nM
16 C6D(+06-11)	5' GGU CUC CUU ACC UAU GA	No skipping
17 H6D(+04-21)	5' UGU CUC AGU AAU CUU CUU ACC UAU	Weak skipping to 50 nM
18 H6D(+18-04)	5' UCU UAC CUA UGA CUA UGG AUG AGA	Very weak skipping to 300 nM

Antisense Oligonucleotides Directed at Exon 4

Antisense oligonucleotides directed at exon 4 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 7 shows an example of a preferred antisense molecule inducing skipping of exon 4 skipping in cultured human cells. In this example, one preferred antisense compound, H4A(+13+32) [SEQ ID NO:19], which targeted a presumed exonic splicing enhancer induced efficient exon skipping at a concentration of 20 nM while other non-preferred antisense oligonucleotides failed to induce even low levels of exon 4 skipping. Another preferred antisense molecule inducing skipping of exon 4 was H4A(+111+40) [SEQ ID NO:22], which induced efficient exon skipping at a concentration of 20 nM.

Table 5 below discloses antisense molecule sequences for inducing exon 4 skipping.

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TABLE 5

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
19	H4A(+13+32)	5' GCA UGA ACU CUU GUG GAU CC	Skipping to 20 nM
22	H4A(+11+40)	5' UGU UCA GGG CAU GAA CUC UUG UGG AUC CUU	Skipping to 20 nM
20	H4D(+04-16)	5' CCA GGG UAC UAC UUA CAU UA	No skipping
21	H4D(-24-44)	5' AUC GUG UGU CAC AGC AUC CAG	No skipping

Antisense Oligonucleotides Directed at Exon 3

Antisense oligonucleotides directed at exon 3 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

15 H3A(+30+60) [SEQ ID NO:23] induced substantial exon 3 skipping when delivered into cells at a concentration of 20 nM to 600 nM. The antisense molecule, H3A(+35+65) [SEQ ID NO: 24] induced exon skipping at 300 nM.

Table 6 below discloses antisense molecule sequences that induce exon 3 skipping.

TABLE 6

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
23	H3A(+30+60)	UAG GAG GCG CCU CCC AUC CUG UAG GUC ACU G	Moderate skipping to 20 to 600 nM
24	H3A(+35+65)	AGG UCU AGG AGG CGC CUC CCA UCC UGU AGG U	Working to 300 nM
25	H3A(+30+54)	GCG CCU CCC AUC CUG UAG GUC ACU G	Moderate 100-600 nM
26	H3D(+46-21)	CUU CGA GGA GGU CUA GGA GGC GCC UC	No skipping
27	H3A(+30+50)	CUC CCA UCC UGU AGG UCA CUG	Moderate 20-600 nM
28	H3D(+19-03)	UAC CAG UUU UUG CCC UGU CAG G	No skipping
29	H3A(-06+20)	UCA AUA UGC UGC UUCCCA AAC UGA AA	No skipping
30	H3A(+37+61)	CUA GGA GGC GCC UCC CAU CCU GUA G	No skipping

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Antisense Oligonucleotides Directed at Exon 5

Antisense oligonucleotides directed at exon 5 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

50 H5A(+20+50) [SEQ ID NO:31] induces substantial exon 5 skipping when delivered into cells at a concentration of 100 nM. Table 7 below shows other antisense molecules tested. The majority of these antisense molecules were not as effective at exon skipping as H5A(+20+50). However, 55 H5A(+15+45) [SEQ ID NO: 40] was able to induce exon 5 skipping at 300 nM.

Table 7 below discloses antisense molecule sequences that induce exon 5 skipping.

TABLE 7

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
31	H5A(+20+50)	UUA UGA UUU CCA UCU ACG AUG UCA GUA CUU C	Working to 100 nM

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TABLE 7-continued

SEQ ID name	Antisense Oligonucleotide Sequence	Ability to induce skipping
32 H5D(+25-05)	CUU ACC UGC CAG UGG AGG AUU AUA UUC CAA A	No skipping
33 H5D(+10-15)	CAU CAG GAU UCU UAC CUG CCA GUG G	Inconsistent at 300 nM
34 H5A(+10+34)	CGA UGU CAG UAC UUC CAA UAU UCA C	Very weak
35 H5D(-04-21)	ACC AUU CAU CAG GAU UCU	No skipping
36 H5D(+16-02)	ACC UGC CAG UGG AGG AUU	No skipping
37 H5A(-07+20)	CCA AUA UUC ACU AAA UCA ACC UGU UAA	No skipping
38 H5D(+18-12)	CAG GAU UCU UAC CUG CCA GUG GAG GAU UAU	No skipping
39 H5A(+05+35)	ACG AUG UCA GUA CUU CCA AUA UUC ACU AAA U	No skipping
40 H5A(+15+45)	AUU UCC AUC UAC GAU GUC AGU ACU UCC AAU A	Working to 300 nM

Antisense Oligonucleotides Directed at Exon 10

Antisense oligonucleotides directed at exon 10 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H10A(-05+16) [SEQ ID NO:41] induced substantial exon 10 skipping when delivered into cells. Table 8 below shows other antisense molecules tested. The antisense molecules ability to induce exon skipping was variable. Table 8 below discloses antisense molecule sequences that induce exon 10 skipping.

TABLE 8

SEQ ID name	Antisense Oligonucleotide Sequence	Ability to induce skipping
41 H10A(-05+16)	CAG GAG CUU CCA AAU GCU GCA	Not tested
42 H10A(-05+24)	CUU GUC UUC AGG AGC UUC CAA AUG CUG CA	Not tested
43 H10A(+98+119)	UCC UCA GCA GAA AGA AGC CAC G	Not tested
44 H10A(+130+149)	UUA GAA AUC UCU CCU UGU GC	No skipping
45 H10A(-33-14)	UAA AUU GGG UGU UAC ACA AU	No skipping

Antisense Oligonucleotides Directed at Exon 11

Antisense oligonucleotides directed at exon 11 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 8B shows an example of H11A(+75+97) [SEQ ID NO:49] antisense molecule inducing exon 11 skipping in cultured human cells. H11A(+75+97) induced substantial exon 11 skipping when delivered into cells at a concentration of 5 nM. Table 9 below shows other antisense molecules tested. The antisense molecules ability to induce exon skipping was observed at 100 nM.

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TABLE 9

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
46	H11D(+26+49)	CCC UGA GGC AUU CCC AUC UUG AAU	Skipping at 100 nM
47	H11D(+11-09)	AGG ACU UAC UUG CUU UGU UU	Skipping at 100 nM
48	H11A(+118+140)	CUU GAA UUU AGG AGA UUC AUC UG	Skipping at 100 nM
49	H11A(+75+97)	CAU CUU CUG AUA AUU UUC CUG UU	Skipping at 100 nM
46	H11D(+26+49)	CCC UGA GGC AUU CCC AUC UUG AAU	Skipping at 5 nM

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Antisense Oligonucleotides Directed at Exon 12

Antisense oligonucleotides directed at exon 12 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H12A(+52+75) [SEQ ID NO:50] induced substantial exon 12 skipping when delivered into cells at a concentration of 5 nM, as shown in FIG. 8A. Table 10 below shows other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. The antisense molecules ability to induce exon skipping was variable.

TABLE 10

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
50	H12A(+52+75)	UCU UCU GUU UUU GUU AGC CAG UCA	Skipping at 5 nM
51	H12A(-10+10)	UCU AUG UAA ACU GAA AAU UU	Skipping at 100 nM
52	H12A(+11+30)	UUC UGG AGA UCC AUU AAA AC	No skipping

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TABLE 11

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
53	H13A(+77+100)	CAG CAG UUG CGU GAU CUC CAC UAG	Skipping at 5 nM
54	H13A(+55+75)	UUC AUC AAC UAC CAC CAC CAU	No skipping
55	H13D(+06-19)	CUA AGC AAA AUA AUC UGA CCU UAA G	No skipping

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Antisense Oligonucleotides Directed at Exon 14

Antisense oligonucleotides directed at exon 14 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Antisense Oligonucleotides Directed at Exon 13

Antisense oligonucleotides directed at exon 13 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H13A(+77+100) [SEQ ID NO:53] induced substantial exon 13 skipping when delivered into cells at a concentration of 5 nM. Table 11 below includes two other antisense

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TABLE 12

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
56	H14A(+37+64)	CUU GUA AAA GAA CCC AGC GGU CUU CUG U	Skipping at 100 nM
57	H14A(+14+35)	CAU CUA CAG AUG UUU GCC CAU C	No skipping
58	H14A(+51+73)	GAA GGA UGU CUU GUA AAA GAA CC	No skipping

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TABLE 12-continued

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
59	H14D(-02+18)	ACC UGU UCU UCA GUA AGA CG	No skipping
60	H14D(+14-10)	CAU GAC ACA CCU GUU CUU CAG UAA	No skipping
61	H14A(+61 +80)	CAU UUG AGA AGG AUG UCU UG	No skipping
62	H14A(-12+12)	AUC UCC CAA UAC CUG GAG AAG AGA	No skipping

Antisense Oligonucleotides Directed at Exon 15

Antisense oligonucleotides directed at exon 15 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H15A(-12+19) [SEQ ID NO:63] and H15A(+48+71) [SEQ ID NO:64] induced substantial exon 15 skipping when delivered into cells at a concentration of 10 nM, as shown in FIG. 9A. Table 13 below includes other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. These other antisense molecules were unable to induce exon skipping at any of the concentrations tested.

TABLE 13

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
63	H15A(-12+19)	GCC AUG CAC UAA AAA GGC ACU GCA AGA CAU U	Skipping at 5 nM
64	H15A(+48+71)	UCU UUA AAG CCA GUU GUG UGA AUC	Skipping at 5 nM
65	H15A(+08+28)	UUU CUG AAA GCC AUG CAC UAA	No skipping
63	H15A(-12+19)	GCC AUG CAC UAA AAA GGC ACU GCA AGA CAU U	No skipping
66	H15D(+17-08)	GUA CAU ACG GCC AGU UUU UGA AGA C	No skipping

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Antisense Oligonucleotides Directed at Exon 16

Antisense oligonucleotides directed at exon 16 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H16A(-12+19) [SEQ ID NO:67] and H16A(-06+25) [SEQ ID NO:68] induced substantial exon 16 skipping when delivered into cells at a concentration of 10 nM, as shown in FIG. 9B. Table 14 below includes other antisense molecules tested. H16A(-06+19) [SEQ ID NO:69] and H16A(+87+109) [SEQ ID NO:70] were tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. These two antisense molecules were able to induce exon skipping at 25 nM and 100 nM, respectively. Additional antisense molecules were tested at 100, 200 and 300 nM and did not result in any exon skipping.

TABLE 14

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
67	H16A(-12+19)	CUA GAU CCG CUU UUA AAA CCU GUU AAA ACA A	Skipping at 5 nM

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TABLE 14-continued

Antisense SEQ ID name	Oligonucleotide Sequence	Ability to induce skipping
68 H16A(-06+25)	UCU UUU CUA GAU CCG CUU UUA AAA CCU GUU A	Skipping at 5 nM
69 H16A(-06+19)	CUA GAU CCG CUU UUA AAA CCU GUU A	Skipping at 25 nM
70 H16A(+87+109)	CCG UCU UCU GGG UCA CUG ACU UA	Skipping at 100 nM
71 H16A(-07+19)	CUA GAU CCG CUU UUA AAA CCU GUU AA	No skipping
72 H16A(-07+13)	CCG CUU UUA AAA CCU GUU AA	No skipping
73 H16A(+12+37)	UGG AUU GCU UUU UCU UUU CUA GAU CC	No skipping
74 H16A(+92+116)	CAU GCU UCC GUC UUC UGG GUC ACU G	No skipping
75 H16A(+45+67)	G AUC UUG UUU GAG UGA AUA CAG U	No skipping
76 H16A(+105+126)	GUU AUC CAG CCA UGC UUC CGU C	No skipping
77 H16D(+05-20)	UGA UAA UUG GUA UCA CUA ACC UGU G	No skipping
78 H16D(+12-11)	GUA UCA CUA ACC UGU GCU GUA C	No skipping

Antisense Oligonucleotides Directed at Exon 19

Antisense oligonucleotides directed at exon 19 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H19A(+35+65) [SEQ ID NO:79] induced substantial exon 19 skipping when delivered into cells at a concentration of 10 nM. This antisense molecule also showed very strong exon skipping at concentrations of 25, 50, 100, 300 and 600 nM.

FIG. 10 illustrates exon 19 and 20 skipping using a "cocktail" of antisense oligonucleotides, as tested using gel electrophoresis. It is interesting to note that it was not easy to induce exon 20 skipping using single antisense oligonucleotides H20A(+44+71) [SEQ ID NO:81] or H20A(+149+170) [SEQ ID NO:82], as illustrated in sections 2 and 3 of the gel shown in FIG. 10. Whereas, a "cocktail" of antisense oligonucleotides was more efficient as can be seen in section 4 of FIG. 10 using a "cocktail" of antisense oligonucleotides H20A(+44+71) and H20A(+149+170). When the cocktail was used to target exon 19, skipping was even stronger (see section 5, FIG. 10).

FIG. 11 illustrates gel electrophoresis results of exon 19/20 skipping using "weasels" The "weasels" were effective in skipping exons 19 and 20 at concentrations of 25, 50, 100, 300 and 600 nM. A further "weasel" sequence is shown in the last row of Table 3C. This compound should give good results.

Antisense Oligonucleotides Directed at Exon 20

Antisense oligonucleotides directed at exon 20 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

None of the antisense oligonucleotides tested induced exon 20 skipping when delivered into cells at a concentration of 10, 25, 50, 300 or 600 nM (see Table 15). Antisense molecules H20A(-11+17) [SEQ ID NO:86] and H20D(+08-20) [SEQ ID NO:87] are yet to be tested.

However, a combination or "cocktail" of H20A(+44+71) [SEQ ID NO: 81] and H20(+149+170) [SEQ ID NO:82] in a ratio of 1:1, exhibited very strong exon skipping at a concentration of 100 nM and 600 nM. Further, a combination of antisense molecules H19A(+35+65) [SEQ ID NO:79], H20A(+44+71) [SEQ ID NO:81] and H20A(+149+170) [SEQ ID NO:82] in a ratio of 2:1:1, induced very strong exon skipping at a concentration ranging from 10 nM to 600 nM.

TABLE 15

Antisense SEQ ID name	Oligonucleotide Sequence	Ability to induce skipping
81 H20A(+44+71)	CUG GCA GAA UUC GAU CCA CCG GCU GUU C	No skipping
82 H20A(+147+168)	CAG CAG UAG UUG UCA UCU GCU C	No skipping
83 H20A(+185+203)	UGA UGG GGU GGU GGG UUG G	No skipping
84 H20A(-08+17)	AUC UGC AUU AAC ACC CUC UAG AAA G	No skipping

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TABLE 15-continued

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
85	H20A(+30+53)	CCG GCU GUU CAG UUG UUC UGA GGC	No skipping
86	H20A(-11+17)	AUC UGC AUU AAC ACC CUC UAG AAA GAA A	Not tested yet
87	H20D(+08-20)	GAA GGA GAA GAG AUU CUU ACC UUA CAA A	Not tested yet
81 & 82	H20A(+44+71) & H20A(+147+168)	CUG GCA GAA UUC GAU CCA CCG GCU GUU C CAG CAG UAG UUG UCA UCU GCU C	Very strong skipping
80, 81 H19A(+35+65); & 82 H20A(+44+71); H20A(+147+168)		GCC UGA GCU GAU CUG CUG GCA UCU UGC AGU U; CUG GCA GAA UUC GAU CCA CCG GCU GUU C; CAG CAG UAG UUG UCA UCU GCU C	Very strong skipping

Antisense Oligonucleotides Directed at Exon 21

Antisense oligonucleotides directed at exon 21 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H21A(+85+108) [SEQ ID NO:92] and H21A(+85+106) [SEQ ID NO:91] induced exon 21 skipping when delivered into cells at a concentration of 50 nM. Table 16 below includes other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping

TABLE 16

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
90	H21A(-06+16)	GCC GGU UGA CUU CAU CCU GUG C	Skips at 600 nM
91	H21A(+85+106)	CUG CAU CCA GGA ACA UGG GUC C	Skips at 50 nM
92	H21A(+85+108)	GUC UGC AUC CAG GAA CAU GGG UC	Skips at 50 nM
93	H21A(+08+31)	GUU GAA GAU CUG AUA GCC GGU UGA	Skips faintly to
94	H21D(+18-07)	UAC UUA CUG UCU GUA GCU CUU UCU	No skipping

Antisense Oligonucleotides Directed at Exon 22

Antisense oligonucleotides directed at exon 22 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 12 illustrates differing efficiencies of two antisense molecules directed at exon 22 acceptor splice site. H22A(+

125+106) [SEQ ID NO:96] and H22A(+80+101) [SEQ ID NO: 98] induce strong exon 22 skipping from 50 nM to 600 nM concentration.

H22A(+125+146) [SEQ ID NO:96] and H22A(+80+101) [SEQ ID NO:98] induced exon 22 skipping when delivered into cells at a concentration of 50 nM. Table 17 below shows other antisense molecules tested at a concentration range of 50, 100, 300 and 600 nM. These antisense molecules showed a variable ability to induce exon skipping.

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TABLE 17

SEQ ID name	Antisense oligonucleotide	Sequence	Ability to induce skipping
95	H22A(+22+45)	CAC UCA UGG UCU CCU GAU AGC GCA	No skipping
96	H22A(+125+146)	CUG CAA UUC CCC GAG UCU CUG C	Skipping to 50 nM
97	H22A(+47+69)	ACU GCU GGA CCC AUG UCC UGA UG	Skipping to 300 nM
98	H22A(+80+101)	CUA AGU UGA GGU AUG GAG AGU	Skipping to 50 nM
99	H22D(+13-11)	UAU UCA CAG ACC UGC AAU UCC CC	No skipping

Antisense Oligonucleotides Directed at Exon 23

Antisense oligonucleotides directed at exon 23 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 18 below shows antisense molecules tested at a concentration range of 25, 50, 100, 300 and 600 nM. These antisense molecules showed no ability to induce exon skipping or are yet to be tested.

TABLE 18

SEQ ID name	Antisense oligonucleotide	Sequence	Ability to induce skipping
100	H23A(+34+59)	ACA GUG GUG CUG AGA UAG UAU AGG CC	No skipping
101	H23A(+18+39)	UAG GCC ACU UUG UUG CUC UUG C	No Skipping
102	H23A(+72+90)	UUC AGA GGG CGC UUU CUU C	No Skipping

Antisense Oligonucleotides Directed at Exon 24

Antisense oligonucleotides directed at exon 24 were prepared using similar methods as described above. Table 19 below outlines the antisense oligonucleotides directed at exon 24 that are yet to be tested for their ability to induce exon 24 skipping.

TABLE 19

SEQ ID name	Antisense oligonucleotide	Sequence	Ability to induce skipping
103	H24A(+48+70)	GGG CAG GCC AUU CCU UCA GA	Needs testing
104	H24A(-02+22)	UCU UCA GGG UUU GUA UGU GAU UCU	Needs testing

Antisense Oligonucleotides Directed at Exon 25

Antisense oligonucleotides directed at exon 25 were prepared using similar methods as described above. Table 20

below shows the antisense oligonucleotides directed at exon 25 that are yet to be tested for their ability to induce exon 25 skipping.

TABLE 20

SEQ ID name	Antisense oligonucleotide	Sequence	Ability to induce skipping
105	H25A(+9+36)	CUG GGC UGA AUU GUC UGA AUA UCA CUG	Needs testing
106	H25A(+131+156)	CUG UUG GCA CAU GUG AUC CCA CUG AG	Needs testing
107	H25D(+16-08)	GUC UAU ACC UGU UGG CAC AUG UGA	Needs testing

Antisense Oligonucleotides Directed at Exon 26

Antisense oligonucleotides directed at exon 26 were prepared using similar methods as described above. Table 21 below outlines the antisense oligonucleotides directed at exon 26 that are yet to be tested for their ability to induce exon 26 skipping.

TABLE 21

SEQ ID name	Antisense oligonucleotide	Sequence	Ability to induce skipping
108	H26A(+132+156)	UGC UUU CUG UAA UUC AUC UGG AGU U	Needs testing
109	H26A(-07+19)	CCU CCU UUC UGG CAU AGA CCU UCC AC	Needs testing
110	H26A(+68+92)	UGU GUC AUC CAU UCG UGC AUC UCU G	Faint skipping at 600 nM

Antisense Oligonucleotides Directed at Exon 27

Antisense oligonucleotides directed at exon 27 were prepared using similar methods as described above. Table 22 below outlines the antisense oligonucleotides directed at exon 27 that are yet to be tested for their ability to induce exon 27 skipping.

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TABLE 22

SEQ ID name	Antisense oligonucleotide Sequence	Ability to induce skipping
111 H27A(+82+106)	UUA AGG CCU CUU GUG CUA CAG GUG G	Needs testing
112 H27A(-4+19)	GGG CCU CUU CUU UAG CUC UCU GA	Faint skipping at 600 and 300 nM
113 H27D(+19-03)	GAC UUC CAA AGU CUU GCA UUU C	v. strong skipping at 600 and 300 nM

Antisense Oligonucleotides Directed at Exon 28 15

Antisense oligonucleotides directed at exon 28 were prepared using similar methods as described above. Table 23 below outlines the antisense oligonucleotides directed at exon 28 that are yet to be tested for their ability to induce exon 28 skipping.

TABLE 23

SEQ ID name	Antisense oligonucleotide Sequence	Ability to induce skipping
114 H28A(-05+19)	GCC AAC AUG CCC AAA CUU CCU AAG	v. strong skipping at 600 and 300 nM
115 H28A(+99+124)	CAG AGA UUU CCU CAG CUC CGC CAG GA	Needs testing
116 H28D(+16-05)	CUU ACA UCU AGC ACC UCA GAG	v. strong skipping at 600 and 300 nM

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Antisense Oligonucleotides Directed at Exon 29

Antisense oligonucleotides directed at exon 29 were prepared using similar methods as described above. Table 24 below outlines the antisense oligonucleotides directed at exon 29 that are yet to be tested for their ability to induce exon 29 skipping.

TABLE 24

SEQ ID name	Antisense oligonucleotide Sequence	Ability to induce skipping
117 H29A(+57+81)	UCC GCC AUC UGU UAG GGU CUG UGC C	Needs testing
118 H29A(+18+42)	AUU UGG GUU AUC CUC UGA AUG UGC C	v. strong skipping at 600 and 300 nM
119 H29D(+17-05)	CAU ACC UCU UCA UGU AGU UCC C	v. strong skipping at 600 and 300 nM

Antisense Oligonucleotides Directed at Exon 30 60

Antisense oligonucleotides directed at exon 30 were prepared using similar methods as described above. Table 25 below outlines the antisense oligonucleotides directed at exon 30 that are yet to be tested for their ability to induce exon 30 skipping.

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TABLE 25

Antisense oligonucleotide SEQ ID name	Sequence	Ability to induce skipping
120 H30A (+122+147)	CAU UUG AGC UGC GUC CAC CUU GUC UG	Needs testing
121 H30A (+25+50)	UCC UGG GCA GAC UGG AUG CUC UGU UC	Very strong skipping at 600 and 300 nM.
122 H30D (+19-04)	UUG CCU GGG CUU CCU GAG GCA UU	Very strong skipping at 600 and 300 nM.

Antisense Oligonucleotides Directed at Exon 31

Antisense oligonucleotides directed at exon 31 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 13 illustrates differing efficiencies of two antisense molecules directed at exon 31 acceptor splice site and a

¹⁵ “cocktail” of exon 31 antisense oligonucleotides at varying concentrations. H31D(+03-22) [SEQ ID NO:124] substantially induced exon 31 skipping when delivered into cells at a concentration of 20 nM. Table 26 below also includes other antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping.

TABLE 26

Antisense oligonucleotide SEQ ID name	Sequence	Ability to induce skipping
123 H31D (+06-18)	UUC UGA AAU AAC AUA UAC CUG UGC	Skipping to 300 nM
124 H31D (+03-22)	UAG UUU CUG AAA UAA CAU AUA CCU G	Skipping to 20 nM
125 H31A (+05+25)	GAC UUG UCA AAU CAG AUU GGA	No skipping
126 H31D (+04-20)	GUU UCU GAA AUA ACA UAU ACC UGU	Skipping to 300 nM

Antisense Oligonucleotides Directed at Exon 32

⁴⁰ Antisense oligonucleotides directed at exon 32 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H32D(+04-16) [SEQ ID NO:127] and H32A(+49+73) ⁴⁵ [SEQ ID NO:130] induced exon 32 skipping when delivered into cells at a concentration of 300 nM. Table 27 below also shows other antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules did not show an ability to induce exon skipping.

TABLE 27

Antisense oligonucleotide SEQ ID name	Sequence	Ability to induce skipping
127H32D (+04-16)	CAC CAG AAA UAC AUA CCA CA	Skipping to 300 nM
128H32A (+151+170)	CAA UGA UUU AGC UGU GAC UG	No skipping
129H32A (+10+32)	CGA AAC UUC AUG GAG ACA UCU UG	No skipping
130H32A (+49+73)	CUU GUA GAC GCU GCU CAA AAU UGG C	Skipping to 300 nM

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Antisense Oligonucleotides Directed at Exon 33

Antisense oligonucleotides directed at exon 33 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 14 shows differing efficiencies of two antisense molecules directed at exon 33 acceptor splice site. H33A(+64+88) [SEQ ID NO:134] substantially induced exon 33 skipping when delivered into cells at a concentration of 10 nM. Table 28 below includes other antisense molecules tested at a concentration of 100, 200 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping.

TABLE 28

SEQ ID name	Antisense oligonucleotide Sequence	Ability to induce skipping
131 H33D (+09-11)	CAU GCA CAC ACC UUU GCU CC	No skipping
132 H33A (+53+76)	UCU GUA CAA UCU GAC GUC CAG UCU	Skipping to 200 nM
133 H33A (+30+56)	GUG UUU AUC ACC AUU UCC ACU UCA GAC	Skipping to 200 nM
134 H33A (+64+88)	GCG UCU GCU UUU UCU GUA CAA UCU G	Skipping to 10 nM

Antisense Oligonucleotides Directed at Exon 34

Antisense oligonucleotides directed at exon 34 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 29 below includes antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping.

TABLE 29

SEQ ID name	Antisense oligonucleotide Sequence	Ability to induce skipping
135 H34A (+83+104)	UCC AUA UCU GUA GCU GGC AGC C	No skipping
136 H34A (+143+165)	CCA GGC AAC UUC AGA AUC CAA AU	No skipping
137 H34A (-20+10)	UUU CUG UUA CCU GAA AAG AAU UAU AAU GAA	Not tested
138 H34A (+46+70)	CAU UCA UUU CCU UUC GCA UCU UAC G	Skipping to 300 nM
139 H34A (+95+120)	UGA UCU CUU UGU CAA UUC CAU AUC UG	Skipping to 300 nM
140 H34D (+10-20)	UUC AGU GAU AUA GGU UUU ACC UUU CCC CAG	Not tested
141 H34A (+72+96)	CUG UAG CUG CCA GCC AUU CUG UCA AG	No skipping

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Antisense Oligonucleotides Directed at Exon 35

Antisense oligonucleotides directed at exon 35 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 15 shows differing efficiencies of antisense molecules directed at exon 35 acceptor splice site. H35A(+24+43) [SEQ ID NO:144] substantially induced exon 35 skipping when delivered into cells at a concentration of 20 nM. Table 30 below also includes other antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules showed no ability to induce exon skipping.

TABLE 30

SEQ ID name	Antisense oligonucleotide	Sequence	Ability to induce skipping
142	H35A (+141+161)	UCU UCU GCU CGG GAG GUG ACA	Skipping to 20 nM
143	H35A (+116+135)	CCA GUU ACU AUU CAG AAG AC	No skipping
144	H35A (+24+43)	UCU UCA GGU GCA CCU UCU GU	No skipping

Antisense Oligonucleotides Directed at Exon 36

Antisense oligonucleotides directed at exon 36 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Antisense molecule H36A(+26+50) [SEQ ID NO:145] induced exon 36 skipping when delivered into cells at a concentration of 300 nM, as shown in FIG. 16.

Antisense Oligonucleotides Directed at Exon 37

Antisense oligonucleotides directed at exon 37 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 17 shows differing efficiencies of two antisense molecules directed at exon 37 acceptor splice site. H37A(+82+105) [SEQ ID NO:148] and H37A(+134+157) [SEQ ID NO:149] substantially induced exon 37 skipping when delivered into cells at a concentration of 10 nM. Table 31 below shows the antisense molecules tested.

TABLE 31

SEQ ID name	Antisense oligonucleotide	Sequence	Ability to induce skipping
147	H37A (+26+50)	CGU GUA GAG UCC ACC UUU GGG CGU A	No skipping
148	H37A (+82+105)	UAC UAA UUU CCU GCA GUG GUC ACC	Skipping to 10 nM
149	H37A (+134+157)	UUC UGU GUG AAA UGG CUG CAA AUC	Skipping to 10 nM

Antisense Oligonucleotides Directed at Exon 38

Antisense oligonucleotides directed at exon 38 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 18 illustrates antisense molecule H38A(+88+112) [SEQ ID NO:152], directed at exon 38 acceptor splice site. H38A(+88+112) substantially induced exon 38 skipping when delivered into cells at a concentration of 10 nM. Table 32 below shows the antisense molecules tested and their ability to induce exon skipping.

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TABLE 32

Antisense SEQ ID name	Sequence	Ability to induce skipping
150H38A (-01+19)	CCU UCA AAG GAA UGG AGG CC	No skipping
151H38A (+59+83)	UGC UGA AUU UCA GCC UCC AGU GGU U	Skipping to 10 nM
152H38A (+88+112)	UGA AGU CUU CCU CUU UCA GAU UCA C	Skipping to 10 nM

Antisense Oligonucleotides Directed at Exon 39

Antisense oligonucleotides directed at exon 39 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H39A(+62+85) [SEQ ID NO:153] induced exon 39 skipping when delivered into cells at a concentration of 100 nM. Table 33 below shows the antisense molecules tested and their ability to induce exon skipping.

TABLE 33

Antisense oligonucleotide SEQ ID name	Sequence	Ability to induce skipping
153 H39A (+62+85)	CUG GCU UUC UCU CAU CUG UGA UUC	Skipping to 100 nM
154 H39A (+39+58)	GUU GUA AGU UGU CUC CUC UU	No skipping
155 H39A (+102+121)	UUG UCU GUA ACA GCU GCU GU	No skipping
156 H39D (+10-10)	GCU CUA AUA CCU UGA GAG CA	Skipping to 300 nM

Antisense Oligonucleotides Directed at Exon 40

Antisense oligonucleotides directed at exon 40 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 19 illustrates antisense molecule H40A(-05+17) [SEQ ID NO:157] directed at exon 40 acceptor splice site. H40A(-05+17) and H40A(+129+153) [SEQ ID NO:158] both substantially induced exon 40 skipping when delivered into cells at a concentration of 5 nM.

Antisense Oligonucleotides Directed at Exon 42

Antisense oligonucleotides directed at exon 42 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 20 illustrates antisense molecule H42A(-04+23) [SEQ ID NO:159], directed at exon 42 acceptor splice site. H42A(-4+23) and H42D(+19-02) [SEQ ID NO:161] both induced exon 42 skipping when delivered into cells at a concentration of 5 nM. Table 34 below shows the antisense molecules tested and their ability to induce exon 42 skipping.

TABLE 34

Antisense oligonucleotide SEQ ID name	Sequence	Ability to induce skipping
159 H42A (-4+23)	AUC GUU UCU UCA CGG ACA GUG UGG UGC	Skipping to 5 nM
160 H42A (+86+109)	GGG CUU GUG AGA CAU GAG UGA UUU	Skipping to 100 nM
161 H42D (+19-02)	A CCU UCA GAG GAC UCC UCU UGC	Skipping to 5 nM

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Antisense Oligonucleotides Directed at Exon 43

Antisense oligonucleotides directed at exon 43 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H43A(+101+120) [SEQ ID NO:163] induced exon 43 skipping when delivered into cells at a concentration of 25 nM. Table 35 below includes the antisense molecules tested and their ability to induce exon 43 skipping.

TABLE 35

SEQ ID name	Antisense oligonucleotide	Sequence	Ability to induce skipping
162	H43D (+10-15)	UAA GUG UUA CCU ACC CUU GUC GGU C	Skipping to 100 nM
163	H43A (+101+120)	GGA GAG AGC UUC CUG UAG CU	Skipping to 25 nM
164	H43A (+78+100)	UCA CCC UUU CCA CAG GCG UUG CA	Skipping to 200 nM

Antisense Oligonucleotides Directed at Exon 44

Antisense oligonucleotides directed at exon 44 were prepared using similar methods as described above. Testing for the ability of these antisense molecules to induce exon 44 skipping is still in progress. The antisense molecules under review are shown as SEQ ID Nos: 165 to 167 in Table 1A.

Antisense Oligonucleotides Directed at Exon 45

Antisense oligonucleotides directed at exon 45 were prepared using similar methods as described above. Testing for the ability of these antisense molecules to induce exon 45 skipping is still in progress. The antisense molecules under review are shown as SEQ ID Nos: 207 to 211 in Table 1A.

Antisense Oligonucleotides Directed at Exon 46

Antisense oligonucleotides directed at exon 46 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 21 illustrates the efficiency of one antisense molecule directed at exon 46 acceptor splice site. Antisense oligonucleotide H46A(+86+115) [SEQ ID NO:203] showed very strong ability to induce exon 46 skipping. Table 36 below includes antisense molecules tested. These antisense molecules showed varying ability to induce exon 46 skipping.

TABLE 36

SEQ ID name	Antisense oligonucleotide	Sequence	Ability to induce skipping
168	H46D (+16-04)	UUA CCU UGA CUU GCU CAA GC	No skipping
169	H46A (+90+109)	UCC AGG UUC AAG UGG GAU AC	No skipping
203	H46A (+86+115)	CUC UUU UCC AGG UUC AAG UGG GAU ACU AGC	Good skipping to 100 nM
204	H46A (+107+137)	CAA GCU UUU CUU UUA GUU GCU GCU CUU UUC C	Good skipping to 100 nM
205	H46A (-10+20)	UAA UCU UUU GUU CUU CUA GCC UGG AGA AAG	Weak skipping
206	H46A (+50+77)	CUG CUU CCU CCA ACC AUA AAA CAA AUU C	Weak skipping

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Antisense Oligonucleotides Directed at Exon 47

Antisense oligonucleotides directed at exon 47 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H47A(+76+100) [SEQ ID NO:170] and H47A(-09+12) [SEQ ID NO:172] both induced exon 47 skipping when delivered into cells at a concentration of 200 nM. H47D(+25-02) [SEQ ID NO: 171] is yet to be prepared and tested.

Antisense Oligonucleotides Directed at Exon 50

Antisense oligonucleotides directed at exon 50 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Antisense oligonucleotide molecule H50A(+02+30) [SEQ ID NO: 173] was a strong inducer of exon skipping. Further, H50A(+07+33) [SEQ ID NO:174] and H50D(+07-18) [SEQ ID NO:175] both induced exon 50 skipping when delivered into cells at a concentration of 100 nM.

Antisense Oligonucleotides Directed at Exon 51

Antisense oligonucleotides directed at exon 51 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 22 illustrates differing efficiencies of two antisense molecules directed at exon 51 acceptor splice site. Antisense oligonucleotide H51A(+66+90) [SEQ ID NO:180] showed the stronger ability to induce exon 51 skipping. Table 37 below includes antisense molecules tested at a concentration range of 25, 50, 100, 300 and 600 nM. These antisense molecules showed varying ability to induce exon 51 skipping. The strongest inducers of exon skipping were antisense oligonucleotide H51A(+61+90) [SEQ ID NO: 179] and H51A(+66+95) [SEQ ID NO: 181].

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TABLE 37

SEQ ID name	Antisense oligonucleotide Sequence	Ability to induce skipping
176 H51A (-01+25)	ACC AGA GUA ACA GUC UGA GUA GGA GC	Faint skipping
177 H51D (+16-07)	CUC AUA CCU UCU GCU UGA UGA UC	Skipping at 300 nM
178 H51A (+111+134)	UUC UGU CCA AGC CCG GUU GAA AUC	Needs re-testing
179 H51A (+61+90)	ACA UCA AGG AAG AUG GCA UUU CUA GUU UGG	Very strong skipping
180 H51A (+66+90)	ACA UCA AGG AAG AUG GCA UUU CUA G	skipping
181 H51A (+66+95)	CUC CAA CAU CAA GGA AGA UGG CAU UUC UAG	Very strong skipping
182 H51D (+08-17)	AUC AUU UUU UCU CAU ACC UUC UGC U	No skipping
183 H51A/D (+08-17) & (-15+?)	AUC AUU UUU UCU CAU ACC UUC UGC UAG GAG CUA AAA	No skipping
184 H51A (+175+195)	CAC CCA CCA UCA GCC UCU GUG	No skipping
185 H51A (+199+220)	AUC AUC UCG UUG AUA UCC UCA A	No skipping

Antisense Oligonucleotides Directed at Exon 52

Antisense oligonucleotides directed at exon 52 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 22 also shows differing efficiencies of four antisense molecules directed at exon 52 acceptor splice site. The most effective antisense oligonucleotide for inducing exon 52 skipping was H52A(+17+37) [SEQ ID NO:188].

Table 38 below shows antisense molecules tested at a concentration range of 50, 100, 300 and 600 nM. These antisense molecules showed varying ability to induce exon 50 skipping. Antisense molecules H52A(+12+41) [SEQ ID NO:187] and H52A(+17+37) [SEQ ID NO:188] showed the strongest exon 50 skipping at a concentration of 50 nM.

TABLE 38

SEQ ID name	Antisense oligonucleotide Sequence	Ability to induce skipping
186H52A (-07+14)	UCC UGC AUU GUU GCC UGU AAG	No skipping
187H52A (+12+41)	UCC AAC UGG GGA CGC CUC UGU UCC AAA UCC	Very strong skipping
188H52A (+17+37)	ACU GGG GAC GCC UCU GUU CCA	Skipping to 50 nM
189H52A (+93+112)	CCG UAA UGA UUG UUC UAG CC	No skipping
190H52D (+05-15)	UGU UAA AAA ACU UAC UUC GA	No skipping

Antisense Oligonucleotides Directed at Exon 53

Antisense oligonucleotides directed at exon 53 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 22 also shows antisense molecule H53A(+39+69) [SEQ ID NO:193] directed at exon 53 acceptor splice site. This antisense oligonucleotide was able to induce exon 53 skipping at 5, 100, 300 and 600 nM. A "cocktail" of three exon 53 antisense oligonucleotides: H53A(+23+47) [SEQ ID NO:195], H53A(+150+176) [SEQ ID NO:196] and H53D(+14-07) [SEQ ID NO:194], was also tested, as shown in FIG. 20 and exhibited an ability to induce exon skipping.

Table 39 below includes other antisense molecules tested at a concentration range of 50, 100, 300 and 600 nM. These antisense molecules showed varying ability to induce exon 53 skipping. Antisense molecule H53A(+39+69) [SEQ ID NO:193] induced the strongest exon 53 skipping.

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TABLE 39

SEQ ID name	Antisense oligonucleotide	Sequence	Ability to induce skipping
191 H53A (+45+69)		CAU UCA ACU GUU GCC UCC GGU UCU G	Faint skipping at 50 nM
192 H53A (+39+62)		CUG UUG CCU CCG GUU CUG AAG GUG	Faint skipping at 50 nM
193 H53A (+39+69)		CAU UCA ACU GUU GCC UCC GGU UCU GAA GGU G	Strong skipping to 50 nM
194 H53D (+14-07)		UAC UAA CCU UGG UUU CUG UGA	Very faint skipping to 50 nM
195 H53A (+23+47)		CUG AAG GUG UUC UUG UAC UUC AUC C	Very faint skipping to 50 nM
196 H53A (+150+176)		UGU AUA GGG ACC CUC CUU CCA UGA CUC	Very faint skipping to 50 nM
197 H53D (+20-05)		CUA ACC UUG GUU UCU GUG AUU UUC U	Not made yet
198 H53D (+09-18)		GGU AUC UUU GAU ACU AAC CUU GGU UUC	Faint at 600 nM
199 H53A (-12+10)		AUU CUU UCA ACU AGA AUA AAA G	No skipping
200 H53A (-07+18)		GAU UCU GAA UUG UUU CAA CUA GAA U	No skipping
201 H53A (+07+26)		AUC CCA CUG AUU CUG AAU UC	No skipping
202 H53A (+124+145)		UUG GCU CUG GCC UGU CCU AAG A	No skipping

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 26

cuucgaggag gucuaggagg cgcuc

26

<210> SEQ ID NO 27
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 27

cucccauccu guaggucacu g

21

<210> SEQ ID NO 28
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 28

uaccaguuuu ugcccuguca gg

22

<210> SEQ ID NO 29
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 29

ucaauaugcu gcuucccaaa cugaaa

26

<210> SEQ ID NO 30
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 30

cuaggaggcg ccucccaucc uguag

25

<210> SEQ ID NO 31
<211> LENGTH: 31
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 31

uuauuuuuuuc caucuacgau gucaguacuu c 31

<210> SEQ ID NO 32
<211> LENGTH: 31
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 32

cuuaccugcc aguggaggau uauauuccaa a 31

<210> SEQ ID NO 33
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 33

caucaggauu cuuaccugcc agugg 25

<210> SEQ ID NO 34
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 34

cgaugucagu acuuccaaua uucac 25

<210> SEQ ID NO 35
<211> LENGTH: 18
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 35

accuucauc aggaauuc 18

<210> SEQ ID NO 36
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 36

accugccagu ggaggauu 18

<210> SEQ ID NO 37

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<211> LENGTH: 27
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 37

ccaauauuca cuaaaucaac cuguuaa 27

<210> SEQ ID NO 38
<211> LENGTH: 30
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 38

caggauucuu accugccagu ggaggauuau 30

<210> SEQ ID NO 39
<211> LENGTH: 31
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 39

acgaugucag uacuuccaau auucacuaaa u 31

<210> SEQ ID NO 40
<211> LENGTH: 31
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 40

auuuccaucu acgaugucag uacuuccaau a 31

<210> SEQ ID NO 41
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 41

caggagcuuc caaaugcugc a 21

<210> SEQ ID NO 42
<211> LENGTH: 29
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 42

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cuugucuca ggagcuucca aaugcugca 29

<210> SEQ ID NO 43
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 43

uccucagcag aaagaagcca cg 22

<210> SEQ ID NO 44
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 44

uuagaaaucu cuccuugugc 20

<210> SEQ ID NO 45
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 45

uaaaauugggu guuacacaau 20

<210> SEQ ID NO 46
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 46

cccugaggca uucccaucuu gaau 24

<210> SEQ ID NO 47
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 47

aggacuacu ugcuuuuuu 20

<210> SEQ ID NO 48
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 48

cuugaaauua ggagauucau cug 23

<210> SEQ ID NO 49
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 49

caucuucuga uaaauuuccu guu 23

<210> SEQ ID NO 50
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 50

ucuucuguuu uuguuagcca guca 24

<210> SEQ ID NO 51
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 51

ucuauguaaa cugaaaauuu 20

<210> SEQ ID NO 52
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 52

uucuggagau ccauuaaaac 20

<210> SEQ ID NO 53
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 53

cagcaguugc gugaucucca cuag 24

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<210> SEQ ID NO 54
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 54

uucaucaacu accaccacca u 21

<210> SEQ ID NO 55
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 55

cuaagcaaaa uaaucugacc uaaag 25

<210> SEQ ID NO 56
<211> LENGTH: 28
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 56

cuuguaaaaag aaccacgagg ucuucugu 28

<210> SEQ ID NO 57
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 57

caucuacaga uguuugccca uc 22

<210> SEQ ID NO 58
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 58

gaaggaguc uuguaaaaga acc 23

<210> SEQ ID NO 59
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

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<400> SEQUENCE: 59

accuguucuu caguaagacg 20

<210> SEQ ID NO 60

<211> LENGTH: 24

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 60

caugacacac cuguucuuca guaa 24

<210> SEQ ID NO 61

<211> LENGTH: 20

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 61

cauuugagaa ggaugucuug 20

<210> SEQ ID NO 62

<211> LENGTH: 24

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 62

aucucccaau accuggagaa gaga 24

<210> SEQ ID NO 63

<211> LENGTH: 31

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 63

gccaugcacu aaaaaggcac ugcaagacau u 31

<210> SEQ ID NO 64

<211> LENGTH: 24

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 64

ucuuuaaagc caguugugug aauc 24

<210> SEQ ID NO 65

<211> LENGTH: 21

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 65

uuucugaaag ccaugcacua a 21

<210> SEQ ID NO 66
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 66

guacauacgg ccaguuuuug aagac 25

<210> SEQ ID NO 67
<211> LENGTH: 31
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 67

cuagauccgc uuuuuuuacc uguuuuuu a 31

<210> SEQ ID NO 68
<211> LENGTH: 31
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 68

ucuuuuuag auccgcuuuu aaaaccuguu a 31

<210> SEQ ID NO 69
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 69

cuagauccgc uuuuuuuacc uguua 25

<210> SEQ ID NO 70
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 70

ccgucuuug ggucacugac uua 23

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<210> SEQ ID NO 71
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 71

cuagauccgc uuuuaaaacc uguuaa 26

<210> SEQ ID NO 72
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 72

ccgcuuuuaa aaccuguuaa 20

<210> SEQ ID NO 73
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 73

uggauugcuu uuucuuuucu agaucc 26

<210> SEQ ID NO 74
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 74

caugcuuccg ucuucugggu cacug 25

<210> SEQ ID NO 75
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 75

gaucuuguuu gagugaauac agu 23

<210> SEQ ID NO 76
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

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<400> SEQUENCE: 76
guuauccagc caugcuuccg uc 22

<210> SEQ ID NO 77
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 77
ugauaaauugg uaucauaac cugug 25

<210> SEQ ID NO 78
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 78
guaucauaa ccugugcugu ac 22

<210> SEQ ID NO 79
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 79
cugcuggcau cuugcaguu 19

<210> SEQ ID NO 80
<211> LENGTH: 31
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 80
gccugagcug aucugcuggc aucugcagu u 31

<210> SEQ ID NO 81
<211> LENGTH: 28
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 81
cuggcagaau ucgauccacc ggcuguuc 28

<210> SEQ ID NO 82
<211> LENGTH: 22
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 82

cagcaguagu ugucaucugc uc 22

<210> SEQ ID NO 83
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 83

ugauggggug guggguugg 19

<210> SEQ ID NO 84
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 84

aucugcauaa acaccucua gaaag 25

<210> SEQ ID NO 85
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 85

ccg'gcguuc aguuguuc aggc 24

<210> SEQ ID NO 86
<211> LENGTH: 28
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 86

aucugcauaa acaccucua gaaagaaa 28

<210> SEQ ID NO 87
<211> LENGTH: 28
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 87

gaaggagaag agauucuac cuuacaaa 28

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<210> SEQ ID NO 88
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 88

auucgaucca ccggcuguuc 20

<210> SEQ ID NO 89
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 89

cagcaguagu ugucaucugc 20

<210> SEQ ID NO 90
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 90

gccgguugac uucauccugu gc 22

<210> SEQ ID NO 91
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 91

cugcauccag gaacaugggu cc 22

<210> SEQ ID NO 92
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 92

gucugcaucc aggaacaugg guc 23

<210> SEQ ID NO 93
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense

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oligonucleotide

<400> SEQUENCE: 93

guugaagauc ugauagccgg uuga 24

<210> SEQ ID NO 94
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 94

uacuuacugu cuguagcucu uucu 24

<210> SEQ ID NO 95
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 95

cacucauggu cuccugauag cgca 24

<210> SEQ ID NO 96
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 96

cugcaauucc ccgagucucu gc 22

<210> SEQ ID NO 97
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 97

acugcuggac ccauguccug aug 23

<210> SEQ ID NO 98
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 98

cuaaguugag guauggagag u 21

<210> SEQ ID NO 99
<211> LENGTH: 23

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 99

uauucacaga ccugcaauuc ccc 23

<210> SEQ ID NO 100
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 100

acaguggugc ugagauagua uaggcc 26

<210> SEQ ID NO 101
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 101

uaggccacuu uguugcucu gc 22

<210> SEQ ID NO 102
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 102

uucagagggc gcuuucuc 19

<210> SEQ ID NO 103
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 103

gggcaggcca uuccuccuuc aga 23

<210> SEQ ID NO 104
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 104

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ucuucaggggu uuguauuguga uucu 24

<210> SEQ ID NO 105
<211> LENGTH: 27
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 105

cugggcugaa uugucugaau aucacug 27

<210> SEQ ID NO 106
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 106

cuguuggcac augugaucac acugag 26

<210> SEQ ID NO 107
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 107

gucuaauaccu guuggcacau guga 24

<210> SEQ ID NO 108
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 108

ugcuuucugu aaaucaucug gaguu 25

<210> SEQ ID NO 109
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 109

ccuccuuucu ggcauagacc uuccac 26

<210> SEQ ID NO 110
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 110

ugugucaucc auucgugcau cucug 25

<210> SEQ ID NO 111
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 111

uuaagccuc uugugcuaca ggugg 25

<210> SEQ ID NO 112
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 112

gggccucuc uuuagcucuc uga 23

<210> SEQ ID NO 113
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 113

gacuuccaaa gucuugcauu uc 22

<210> SEQ ID NO 114
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 114

gccaacaugc ccaaacuucc uaag 24

<210> SEQ ID NO 115
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 115

cagagauuuc cucagcuccg ccagga 26

<210> SEQ ID NO 116

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<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 116

cuuacaucua gcaccucaga g 21

<210> SEQ ID NO 117
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 117

uccgccaucu guuagggucu gugcc 25

<210> SEQ ID NO 118
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 118

auuuggguua uccucugaau gucgc 25

<210> SEQ ID NO 119
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 119

cauaccucuu cauguaguuc cc 22

<210> SEQ ID NO 120
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 120

cauuugagcu gcguccaccu ugucug 26

<210> SEQ ID NO 121
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 121

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uccugggcag acuggaugcu cuguuc 26

<210> SEQ ID NO 122
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 122

uugccugggc uuccugaggc auu 23

<210> SEQ ID NO 123
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 123

uucugaaaua acauauaccu gugc 24

<210> SEQ ID NO 124
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 124

uaguuuucuga aaauacauau accug 25

<210> SEQ ID NO 125
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 125

gacuugucua aucagauugg a 21

<210> SEQ ID NO 126
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 126

guuucugaaa uaacauauac cugu 24

<210> SEQ ID NO 127
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 127

caccagaaau acauaccaca 20

<210> SEQ ID NO 128
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 128

caaugauuuu gcugugacug 20

<210> SEQ ID NO 129
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 129

cgaaacuca uggagacau uug 23

<210> SEQ ID NO 130
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 130

cuuguagacg cugcucaaaa uggc 25

<210> SEQ ID NO 131
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 131

caugcacaca ccuugcucc 20

<210> SEQ ID NO 132
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 132

ucuguacaau cugacgucca gucu 24

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<210> SEQ ID NO 133
 <211> LENGTH: 27
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Human 2'-O-methyl phosphorothioate antisense
 oligonucleotide

<400> SEQUENCE: 133

gucuuuauca ccauuuccac uucagac 27

<210> SEQ ID NO 134
 <211> LENGTH: 25
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Human 2'-O-methyl phosphorothioate antisense
 oligonucleotide

<400> SEQUENCE: 134

ccgucugcuu uuucuguaca aucug 25

<210> SEQ ID NO 135
 <211> LENGTH: 22
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Human 2'-O-methyl phosphorothioate antisense
 oligonucleotide

<400> SEQUENCE: 135

uccauaucug uagcugccag cc 22

<210> SEQ ID NO 136
 <211> LENGTH: 23
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Human 2'-O-methyl phosphorothioate antisense
 oligonucleotide

<400> SEQUENCE: 136

ccaggcaacu ucagaaucca aa 23

<210> SEQ ID NO 137
 <211> LENGTH: 30
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Human 2'-O-methyl phosphorothioate antisense
 oligonucleotide

<400> SEQUENCE: 137

uuucuguuac cugaaaagaa uuuaaagaa 30

<210> SEQ ID NO 138
 <211> LENGTH: 25
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Human 2'-O-methyl phosphorothioate antisense
 oligonucleotide

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<400> SEQUENCE: 138
cauucuuuuc cuuucgcauc uuacg 25

<210> SEQ ID NO 139
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 139
ugaucucuuu gucaauucca uaucug 26

<210> SEQ ID NO 140
<211> LENGTH: 30
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 140
uucaguguaa uagguuuuac cuuuccccag 30

<210> SEQ ID NO 141
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 141
cuguagcugc cagccauucg gucaag 26

<210> SEQ ID NO 142
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 142
ucuucugcuc gggaggugac a 21

<210> SEQ ID NO 143
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 143
ccaguacua uucagaagac 20

<210> SEQ ID NO 144
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 144

ucuucaggug caccuucugu 20

<210> SEQ ID NO 145
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 145

ugugaugugg uccacauucu ggua 25

<210> SEQ ID NO 146
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 146

ccauguguuu cugguauucc 20

<210> SEQ ID NO 147
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 147

cguguagagu ccaccuuugg gcgua 25

<210> SEQ ID NO 148
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 148

uacuaauuuc cugcaguggu cacc 24

<210> SEQ ID NO 149
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 149

uucuguguga aauggcugca aauc 24

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<210> SEQ ID NO 150
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      Human 2'-O-methyl phosphorothioate antisense
      oligonucleotide

<400> SEQUENCE: 150

ccuucaaaagg aauggaggcc                20

<210> SEQ ID NO 151
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      Human 2'-O-methyl phosphorothioate antisense
      oligonucleotide

<400> SEQUENCE: 151

ugcugaaauu cagccuccag ugguu          25

<210> SEQ ID NO 152
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      Human 2'-O-methyl phosphorothioate antisense
      oligonucleotide

<400> SEQUENCE: 152

ugaagucuuc cucuuucaga uucac          25

<210> SEQ ID NO 153
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      Human 2'-O-methyl phosphorothioate antisense
      oligonucleotide

<400> SEQUENCE: 153

cuggcuuucu cucaucugug auuc          24

<210> SEQ ID NO 154
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 154

guuguaaguu gucuccucuu                20

<210> SEQ ID NO 155
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      Human 2'-O-methyl phosphorothioate antisense
      oligonucleotide

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<400> SEQUENCE: 155

uugucuguaa cagcugcugu 20

<210> SEQ ID NO 156

<211> LENGTH: 20

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 156

gcucuaauac cuugagagca 20

<210> SEQ ID NO 157

<211> LENGTH: 22

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 157

cuuugagacc ucaaaucug uu 22

<210> SEQ ID NO 158

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 158

cuuuuuuuc cuuucaucuc ugggc 25

<210> SEQ ID NO 159

<211> LENGTH: 27

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 159

aucguuucuu cacggacagu gugcugg 27

<210> SEQ ID NO 160

<211> LENGTH: 24

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 160

gggcuuguga gacaugagug auuu 24

<210> SEQ ID NO 161

<211> LENGTH: 22

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Human 2'-O-methyl phosphorothioate antisense
 oligonucleotide

<400> SEQUENCE: 161

accuucagag gacuccucuu gc 22

<210> SEQ ID NO 162
 <211> LENGTH: 25
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Human 2'-O-methyl phosphorothioate antisense
 oligonucleotide

<400> SEQUENCE: 162

uauguguuac cuaccuuugu cgguc 25

<210> SEQ ID NO 163
 <211> LENGTH: 20
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Human 2'-O-methyl phosphorothioate antisense
 oligonucleotide

<400> SEQUENCE: 163

ggagagagcu uccuguagcu 20

<210> SEQ ID NO 164
 <211> LENGTH: 23
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Human 2'-O-methyl phosphorothioate antisense
 oligonucleotide

<400> SEQUENCE: 164

ucacccuuuc cacaggcguu gca 23

<210> SEQ ID NO 165
 <211> LENGTH: 20
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Human 2'-O-methyl phosphorothioate antisense
 oligonucleotide

<400> SEQUENCE: 165

uuugugucuu ucugagaaac 20

<210> SEQ ID NO 166
 <211> LENGTH: 20
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Human 2'-O-methyl phosphorothioate antisense
 oligonucleotide

<400> SEQUENCE: 166

aaagacuuac cuuaagauac 20

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<210> SEQ ID NO 167
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 167

aucugucaaa ucgccugcag 20

<210> SEQ ID NO 168
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 168

uuaccuugac uugcucaagc 20

<210> SEQ ID NO 169
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 169

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<210> SEQ ID NO 170
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oligonucleotide

<400> SEQUENCE: 170

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<210> SEQ ID NO 171
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<400> SEQUENCE: 171

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<400> SEQUENCE: 172
uuccaccagu aacugaaaca g 21

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<210> SEQ ID NO 176
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<400> SEQUENCE: 176
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<210> SEQ ID NO 177
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<400> SEQUENCE: 177
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<210> SEQ ID NO 178
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<213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 Human 2'-O-methyl phosphorothioate antisense
 oligonucleotide

<400> SEQUENCE: 178

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 Human 2'-O-methyl phosphorothioate antisense
 oligonucleotide

<400> SEQUENCE: 179

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 oligonucleotide

<400> SEQUENCE: 180

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 oligonucleotide

<400> SEQUENCE: 181

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 oligonucleotide

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 Human 2'-O-methyl phosphorothioate antisense
 oligonucleotide

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oligonucleotide

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oligonucleotide

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oligonucleotide

<400> SEQUENCE: 188

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Human 2'-O-methyl phosphorothioate antisense

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oligonucleotide

<400> SEQUENCE: 189

ccguaaugau uguucuagcc 20

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oligonucleotide

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uacuaaccuu gguuucug a 21

<210> SEQ ID NO 195
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<400> SEQUENCE: 197

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<400> SEQUENCE: 200

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gauucugaau ucuuuaacu agaau 25

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oligonucleotide

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Human 2'-O-methyl phosphorothioate antisense
oligonucleotide

<400> SEQUENCE: 206

cugcuuccuc caaccuauaa acaaaauuc 28

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 214

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What is claimed is:

1. An antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69), wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide induces exon 53 skipping; or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 20 to 31 bases comprising a base

sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69), wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide induces exon 53 skipping, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

* * * * *

ATTACHMENT F

PTO/AIA/26 (04-14)

Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

**TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING
REJECTION OVER A "PRIOR" PATENT**

Docket Number (Optional)

4140.01500A9

In re Application of: The University of Western Australia

Application No.: 15/705,172

Filed: September 14, 2017

For: ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF
USE THEREOF

The applicant, The University of Western Australia, owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent No. 8,232,384 B2 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 58,403

Marsha Rose Gillentine April 3, 2018
Signature Date

Marsha Rose Gillentine

Typed or printed name

Director

Title

(202) 371-2600

Telephone Number

- ☒ Terminal disclaimer fee under 37 CFR 1.20(d) included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

This collection of information is required by 37 CFR 1.321. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

9204086

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

SRPT-VYDS-0005168

ATTACHMENT G

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 9,994,851 B2
APPLICATION NO. : 15/705172
DATED : June 12, 2018
INVENTOR(S) : Wilton et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

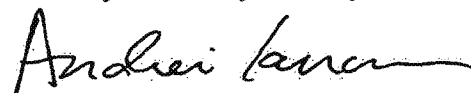
In the Specification

Column 1, Line 26, before "STATEMENT REGARDING SEQUENCE LISTING", insert:

--STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

This invention was made with government support under grant number R01 NS044146 awarded by the National Institutes of Health. The government has certain rights in the invention.--

Signed and Sealed this
Thirty-first Day of July, 2018



Andrei Iancu
Director of the United States Patent and Trademark Office

ATTACHMENT H



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 119982

**IND AND FAST TRACK REQUEST
ACKNOWLEDGEMENT**

Sarepta Therapeutics, Inc.
Attention: Matthew Rael, MS
Manager, Regulatory Affairs
215 First Street, Suite 415
Cambridge, MA 02142

Dear Mr. Rael:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA). Please note the following identifying data:

IND NUMBER ASSIGNED:	119982
SPONSOR:	Sarepta Therapeutics, Inc.
PRODUCT NAME(S):	SRP-4053
DATE OF SUBMISSION:	November 7, 2014
DATE OF RECEIPT:	November 7, 2014
PROPOSED INDICATION:	Treatment of patients with Duchenne muscular dystrophy amenable to exon 53 skipping

You may not initiate studies in humans until 30 days after the date of receipt shown above unless we notify you sooner that you may proceed. If, on or before December 7, 2014, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will immediately notify you verbally or in writing that (1) clinical studies may not be initiated under this IND ("clinical hold") or (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). If we place your human studies on clinical hold, you will be notified in writing of the reasons and the information necessary to correct the deficiencies. In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have subsequently notified you that the information you submitted is satisfactory.

IND 119982
Page 2

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

ACKNOWLEDGE FAST TRACK REQUEST

We also acknowledge receipt on November 7, 2014, of your November 7, 2014, request for Fast Track designation submitted under section 506 of the Act for the treatment of patients with Duchenne muscular dystrophy amenable to exon 53 skipping. We are reviewing your request and will respond to you within 60 days of the receipt date.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:
<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA>

IND 119982
Page 3

[ct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm](http://www.fda.gov/oc/significantamendments-to-the-fdc-act/food-and-drug-administration-amendments-act-of-2007/ucm095442.htm). Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **IND 119982** submitted on November 7, 2014, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

ADDITIONAL IND RESPONSIBILITIES

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

If your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

If your IND is not in eCTD format:

- you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;
- if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);
- if you also send copies of these reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as "Duplicate."
- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information

IND 119982
Page 4

qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format via the ESG. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND became active (the date clinical studies were permitted to begin) [21 CFR 312.33].

CHARGING FOR AN INVESTIGATIONAL DRUG

We remind you that, under 21 CFR 312.8(a)(3), you may not charge for this investigational drug without prior written authorization from FDA.

GOOD LABORATORY PRACTICE

All laboratory or animal studies intended to support the safety of this product should be conducted in compliance with the regulations for "Good Laboratory Practice for Nonclinical Laboratory Studies" (21 CFR 58). If such studies have not been conducted in compliance with these regulations, provide a statement describing in detail all differences between the practices used and those required in the regulations.

ENVIRONMENTAL ASSESSMENT

Box 13, item 7 of form FDA 1571 requests that either an "environmental assessment," or a "claim for categorical exclusion" from the requirements for environmental assessment, be included in the IND. If you did not include a response to this item with your application, please submit one. Information on environmental assessments is available in the guidance "Environmental Assessment of Human Drugs and Biologics." This document is available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070561.pdf>.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

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Page 5

PEDIATRIC ASSESSMENTS

As amended by the Food and Drug Administration Safety and Innovation Act (Public Law 112-144, 126 Stat. 993) of July 9, 2012, the Pediatric Research Equity Act (PREA) requires any sponsor who plans to file a marketing application for a drug or biological product (FDCA section 505 or PHSA section 351, respectively) that includes a new active ingredient, new indication, new dosage form, new dosing regimen, and/or new route of administration to submit an initial Pediatric Study Plan (PSP) (21 U.S.C. 355c). The intent of the PSP is to identify needed pediatric studies and begin planning for these studies. The timing and content of an initial PSP, including a template, can be found at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. Review this guidance and the PREA requirements to determine if your application must contain an assessment (pediatric clinical data), waiver request, and/or deferral request (21 U.S.C. 355c).

If you have any questions, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov.

SUBMISSION REQUIREMENTS

Cite the IND number listed above at the top of the first page of any communications concerning this application. Each submission to this IND must be provided in triplicate (original plus two copies). Please include three originals of all illustrations that do not reproduce well. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient

IND 119982
Page 6

information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/>.

If you have any questions, please contact me by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Fannie Choy, R.Ph.
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YUET L CHOY
11/17/2014

ATTACHMENT I



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 119982

REMOVE FULL CLINICAL HOLD

Sarepta Therapeutics, Inc.
Attention: Matthew Curtis
Director of Regulatory Affairs
215 First Street, Suite 415
Cambridge, MA 02142

Dear Mr. Curtis:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SRP-4053.

We also refer to your amendment dated December 29, 2015, that provides a complete response to our Full Clinical Hold letter of December 18, 2015, which cited the reasons for placing this IND on clinical hold and the information needed to resolve the clinical hold issues.

We further refer to your electronic communication of January 28, 2016, in response to our request of January 28, 2016, to revise the Informed Consent and Assent Forms for Study 4045-301. We note your commitment to make the changes as requested and to submit the final documents officially to the IND as soon as possible.

We have completed the review of your submissions and have concluded that the clinical trials may be resumed.

ADDITIONAL IND RESPONSIBILITIES

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

If your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

If your IND is not in eCTD format:

IND 119982

Page 2

- you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;
- if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);
- if you also send copies of these reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as "Duplicate."
- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and
- Submitting annual progress reports within 60 days of the anniversary of the date that the IND became active (the most recent date when clinical studies were permitted to begin) [21 CFR 312.33]. If your IND previously had an harmonized annual report due date, it is no longer valid and therefore you will need to submit a new request.

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/>.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Billy Dunn, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC P BASTINGS

01/28/2016

Signed for Dr. Dunn

ATTACHMENT J



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 211970

NDA ACKNOWLEDGMENT

Sarepta Therapeutics, Inc.
Attention: Patrick O'Malley
Executive Director, Regular Affairs
215 First Street, Suite 415
Cambridge, MA 02142

Dear Mr. O'Malley:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug: Golodirsén injection, 50 mg/mL

Date of Application: December 19, 2018

Date of Receipt: December 19, 2018

Our Reference Number: NDA 211970

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 17, 2019, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

Cite the NDA reference number at the top of each page of any submission related to this marketing application.

NDA 211970
Page 2

SUBMISSION REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File and Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>.

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, contact me at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Fannie Choy, R.Ph.
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

YUET L CHOY
01/03/2019 10:52:53 AM

ATTACHMENT K

Chronology of Events on VYONDYS 53™

NDA 211970

The table below lists significant communication with FDA during VYONDYS 53™ review from the IND submission to the final NDA approval in descending order

Date	Submission Activity Name	Application	Summary
11/7/2014	Original IND 119982	IND 119982	
11/16/2014	[REDACTED]-fda-letter-ind fast-track-acknowledgement.pdf	IND 119982	FDA's Acknowledgment with receipt of IND and Fast track Designation
11/30/2014	[REDACTED]-fda-email-03dec14-internal-safety-review-mtg.pdf	IND 119982	FDA requesting SRPT to be on stand by as they have a scheduled an internal safety review meeting to discuss your pending IND 119982 on Wed 12/3/14 at 3 pm
12/1/2014	[REDACTED]-fda-email-ackn-rcpt.pdf	IND 119982	FDA acknowledging receipt of email
12/1/2014	[REDACTED]-srpt-email-tcon-dial-in.pdf	IND 119982	SRPT providing FDA the T-Con numbers for Dec 3rd
12/2/2014	[REDACTED]-fda-email-no-comments-or-questions.pdf	IND 119982	FDA letting SRPT know that they had no comments or questions during meeting
12/2/2014	[REDACTED]-fda-email-still-in-discussion.pdf	IND 119982	FDA letting SRPT know they are still discussing
12/2/2014	[REDACTED]-srpt-email-dialed-in-now.pdf	IND 119982	SRPT letting FDA know they are in dialed in for the t-con post meeting
12/2/2014	[REDACTED]-srpt-email-thanks.pdf	IND 119982	SRPT acknowledging FDA's email
12/4/2014	[REDACTED]-fda-email-comments-on-ib.pdf	IND 119982	Reference is made to your IND 119982 for SRP-4053. We also refer to your submission of November 7, 2014. I am forwarding the following request from the review team. [REDACTED]

Date	Submission Activity Name	Application	Summary
			[REDACTED]
12/4/2014	[REDACTED]-srpt-email-ackn-rcpt.pdf	IND 119982	SRPT acknowledging receipt of email from FDA
12/10/2014	[REDACTED]-fda-letter-fast-track-granted.pdf	IND 119982	FDA's letter granting Fast Track Designation
12/12/2014	[REDACTED]-srpt-email-ib-response.pdf	IND 119982	SRPT providing FDA with the responses for comments recieved on the 5th Dec and the proposed changes to the IB
2/9/2015	[REDACTED]-fda-email-rqst-icf.pdf	IND 119982	Reference is made to your IND 119982 for SRP-4053. I am forwarding the following request for the review team. We ask that you submit the current informed consent document for IND 119982. If it has previously been submitted, we ask that you direct us to its location in the IND.
2/11/2015	[REDACTED]-srpt-email-ackn-rcpt (2).pdf	IND 119982	
3/17/2015	[REDACTED]-fda-email-rqst-human-pk-summary.pdf	IND 119982	Reference is made to your IND 119982 for SRP-4053. I am sending the following information request on behalf of the review team: [REDACTED]
3/17/2015	[REDACTED]-srpt-email-ackn-rcpt.pdf	IND 119982	
4/1/2015	[REDACTED]-srpt-roc-pnda-bd-image-proposal-and-804-protocol(3).pdf	IND 119982	

Date	Submission Activity Name	Application	Summary
4/1/2015	[REDACTED]-srpt-email-dystrophin-image-proposal-and-804-protocol(3).pdf	IND 119982	
5/3/2015	[REDACTED]-srpt-roc-4053-investigational-plan.pdf	IND 119982	
5/19/2015	[REDACTED]-fda-email-clinical-irs.pdf	IND 119982	Reference is made to your IND 119982 for SRP-4053. I am sending the following information request on behalf of the review team: [REDACTED]
5/19/2015	[REDACTED]-srpt-email-ackn-rcpt.pdf	IND 119982	
5/28/2015	[REDACTED]-fda-email-inq-responses-to-20may15-clinical-irs.pdf	IND 119982	
5/28/2015	[REDACTED]-srpt-email-ackn-rcpt.pdf	IND 119982	
6/1/2015	[REDACTED]-srpt-email-response-to-20may15-clinical-irs.pdf	IND 119982	
6/1/2015	[REDACTED]-fda-email-inq-response-by-cob-today.pdf	IND 119982	
6/1/2015	[REDACTED]-fda-email-ackn-rcpt.pdf	IND 119982	
6/30/2015	[REDACTED]-srpt-email-inq-clinical-hold-letter.pdf	IND 119982	
7/23/2015	[REDACTED]-fda-efax-full-clinical-hold.pdf	IND 119982	Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SRP-4053. [REDACTED]

Date	Submission Activity Name	Application	Summary
			[REDACTED]
7/23/2015	[REDACTED]-srpt-email-ackn-rcpt.pdf	IND 119982	
7/23/2015	[REDACTED]-srpt-email-inq-clinical-hold-letter.pdf	IND 119982	
10/5/2015	[REDACTED]-srpt-contact-rpt-fda-tcon-min.pdf	IND 119982	
10/25/2015	[REDACTED]-srpt-email-how-is-complete-response-review-going.pdf	IND 119982	
10/26/2015	[REDACTED]-fda-email-we-need-srpt-on-standby-during-hold-rev-mtg.pdf	IND 119982	
10/26/2015	[REDACTED]-fda-email [REDACTED]-confirm-prot-ver-ind119982.pdf	IND 119982	FDA request to confirm submission of recent version of the [REDACTED] protocol to [REDACTED] and IND 119982 (seq. 0004) on April 3, 2015
10/27/2015	[REDACTED]-srpt-email-srpt-will-be-on-standby-cr-questions.pdf	IND 119982	
10/27/2015	[REDACTED]-srpt-email-4053-301-amendment-versions.pdf	IND 119982	
10/27/2015	[REDACTED]-fda-email-most-recent-version-of-301-submitted.pdf	IND 119982	
11/3/2015	[REDACTED]-fda-email-will-not-call-into-conference.pdf	IND 119982	
11/3/2015	[REDACTED]-srpt-email [REDACTED]-central-port-Oct15-tcon-min.pdf	IND 119982	Email Sponsor meeting minutes from 06Oct2016 teleconference discussing central port use in the

Date	Submission Activity Name	Application	Summary
			placebo population for the [REDACTED] clinical study
11/3/2015	[REDACTED]-srpt-4053-complete-response-follow-up-t-con-request-call-in-number.pdf	IND 119982	
11/5/2015	[REDACTED]-srpt-email-ack-rcpt-email-ind-119982.pdf	IND 119982	
11/8/2015	[REDACTED]-fda-srp-4053-prot-[REDACTED] [REDACTED]-remains-on-clin-hold.pdf	IND 119982	We have completed the review of your submission and have concluded that removal of the clinical hold is not warranted. [REDACTED]

Date	Submission Activity Name	Application	Summary
			[REDACTED]
11/8/2015	[REDACTED]-srpt-ind-4053- acknowledge-4053-301-remains-	IND 119982	[REDACTED]

Date	Submission Activity Name	Application	Summary
	on-clin-hold.pdf		
12/17/2015	[REDACTED]-fda-letter-continue-4053-clin-hold.pdf	IND 119982	We also refer to your amendment dated November 18, 2015, that provides a response to our Continue Full Clinical Hold letter of November 6, 2015, which cited the reasons this IND was placed on clinical hold and the information needed to resolve the clinical hold issues. [REDACTED]
12/17/2015	[REDACTED]-fda-email-4053-re-clin-hold-ind119982.pdf	IND 119982	FDA: Attached please find an electronic copy of the letters for [REDACTED] IND 119982, responding to the submissions of November 18, 2015.
12/17/2015	[REDACTED]-srpt-email-ind-status.pdf	[REDACTED] IND 119982	Thank you to FDA for letters responding to the November 18, 2015 submissions
12/22/2015	[REDACTED]-fda-email-recd-4053-ibcant-agree-to-commence-clock-today.pdf	IND 119982	
12/22/2015	[REDACTED]-srpt-email-courtesy-copy-4053-ib-icf-assent.pdf	IND 119982	
12/22/2015	[REDACTED] srpt-email-response-to-clinical-hold.pdf	IND 119982	Response to Clinical Hold 4053-301
12/30/2015	[REDACTED]-fda-email-4053-response-to-clin-hold-request-for-icf-ind119983.pdf	IND 119982	Request from FDA to send via email the Word version of Informed Consent Form and Assent Form at your earliest convenience.
12/30/2015	[REDACTED]-srpt-email-icf-assent-forms.pdf	IND 119982	Email response to FDA to send via email the Word version of Informed Consent Form and Assent Form at your earliest convenience.
1/26/2016	[REDACTED]-fda-email-4053-comments-to-sponsor-ind119982.pdf	IND 119982	FDA comments on the informed consent for protocol [REDACTED] Request to return the documents to FDA for review by 1200 noon EST on Thursday January 28, 2016.
1/26/2016	[REDACTED]-srpt-email-thank-you.pdf	IND 119982	Sarepta thank you/acknowledgement of RFI regarding Informed Consent 27Jan2016

Date	Submission Activity Name	Application	Summary
1/27/2016	██████-fda-letter-4053-safe-to-proceed.pdf	IND 119982	Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SRP-4053. We also refer to your amendment dated December 29, 2015, that provides a complete response to our Full Clinical Hold letter of December 18, 2015, which cited the reasons for placing this IND on clinical hold and the information needed to resolve the clinical hold issues. We further refer to your electronic communication of January 28, 2016, in response to our request of January 28, 2016, to revise the Informed Consent and Assent Forms for Study ██████. We note your commitment to make the changes as requested and to submit the final documents officially to the IND as soon as possible. We have completed the review of your submissions and have concluded that the clinical trials may be resumed.
1/27/2016	██████-fda-email-4053-comments-to-sponsor-ind119982.pdf	IND 119982	Email string with FDA regarding the formal submission of the proposed Informed Consent and Assent Forms
1/27/2016	██████-srpt-email-revised-icf-assent-forms.pdf	IND 119982	Sarepta email of the revised Informed Consent and Assent Forms for Study ██████
1/27/2016	██████-srpt-email-thank-you-b.pdf	IND 119982	Thank you for FDA for clarification on submission of the proposed Informed Consent and Assent Forms
1/27/2016	██████-srpt-email-thank-you-a.pdf	IND 119982	Thank you to ██████ at FDA for heads up that a request will be coming
1/28/2016	██████-fda-letter-4053-remove-clinical-hold-ind119982.pdf	IND 119982	FDA letter to remove full clinical hold for Study ██████, FDA requests that the proposed Informed Consent and Assent Forms be formally submitted
7/25/2016	██████-srpt-email-fda-4053-nda211970-proposed-labeling-text.pdf	NDA 211970	sarepta would like clarification on proposed labeling text received from agency as they do not seem to align with data
8/30/2016	██████-srpt-email-rqst-ind-annual-reporting-period-change.pdf	IND 119982	
9/6/2016	██████-fda-email-approve-ind-annual-reporting-period-change.pdf	IND 119982	
3/9/2017	██████-srpt-email ██████ chronic-tox-study-response.pdf	IND 119982	Email response to FDA info request, Regarding ██████ for ██████

Date	Submission Activity Name	Application	Summary
			[REDACTED]
3/16/2017	[REDACTED]-srpt-email-advisory-mtg-notification-essence-response-nct02500381.pdf	[REDACTED];#IND 119982	Email string between Sarepta and FDA regarding teleconference prior to May 18 to review the federal panel review (to evaluate [REDACTED] 4053 protocol) under 21 CFR 50.54 process and discuss our involvement in the meeting
3/20/2017	[REDACTED]-srpt-email-updated-ra-contacts-ind119982.pdf	IND 119982	Provided updated RA contacts
3/20/2017	[REDACTED]-srpt-email-updated-racmc-contacts-ind119982.pdf	IND 119982	Provided updated RA contacts
3/29/2017	[REDACTED]-fda-email-mtg [REDACTED] - SRP-4053 -dmd-patients-essence-nct02500381.pdf	[REDACTED];#IND 119982	FDA Information Request referencing the draft protocol, submitted on January 27, 2017, for Study SR-17-012 and PMR 3095-4 cited in NDA approval letter
4/3/2017	[REDACTED]-fda-email-agency-breakdown [REDACTED] -4053-discussion.pdf	[REDACTED];#IND 119982	Meeting with Sarepta to discuss the [REDACTED] and SRP-4053 in DMD Patients (ESSENCE) - NCT02500381 - Agency breakdown of 3 April 2017 discussion with Sarepta.
4/6/2017	[REDACTED]-fda-email-peds-adcom-to-discuss-essence-ports.pdf	[REDACTED];#IND 119982	Meeting with Sarepta to discuss the [REDACTED] and SRP-4053 in DMD Patients (ESSENCE) - NCT02500381 - Discussion after meeting
5/1/2017	[REDACTED]-srpt-email-ind [REDACTED] 119982-waiver-&-redacted-docs-18may17-pac-pes	[REDACTED];#IND 119982	Waiver and Redacted documents for 18 May 2017 PAC-PES. Attachments: [REDACTED]
5/1/2017	[REDACTED]	[REDACTED];#IND 119982	
5/1/2017	[REDACTED]	[REDACTED];#IND 119982	
5/1/2017	[REDACTED]	[REDACTED];#IND 119982	
5/1/2017	[REDACTED]	[REDACTED];#IND 119982	

Date	Submission Activity Name	Application	Summary
5/1/2017	[REDACTED]	[REDACTED];#IND 119982	
5/1/2017	[REDACTED]	[REDACTED];#IND 119982	
5/1/2017	[REDACTED]	[REDACTED];#IND 119982	
5/1/2017	[REDACTED]	[REDACTED];#IND 119982	
5/1/2017	[REDACTED]	[REDACTED];#IND 119982	
5/7/2017	[REDACTED]-fda-email-updated-redactions-pac-pes-meeting.pdf	[REDACTED];#IND 119982	Updated Redactions for PAC-PES Meeting. Sarepta also provided "marked for redaction" versions of [REDACTED]
5/10/2017	[REDACTED]-srpt-email-essence-pac-slides-and-attendees.pdf	[REDACTED];#IND 119982	Badging Requirements for the PES/PAC with Attachment: FDA PAC-PES Sponsor Slides (11May2017)
5/29/2017	[REDACTED]-fda-email-fda-determination-letter [REDACTED].pdf	[REDACTED];#IND 119982	String - Recommendation for Permitting the Use of a Totally Implantable Central Venous Access Device in the [REDACTED] Protocol
7/10/2017	[REDACTED]-fda-email-comments-to-sponsor-[REDACTED]-srp4053-protocol-v6.pdf	[REDACTED];#IND 119982	FDA provided comments for the [REDACTED] Protocol consent regarding TICVAD statement
7/17/2017	[REDACTED]-fda-email-request-[REDACTED]-53-study-status-53.pdf	IND 119982	FDA Information Request - Status of Ongoing Phase 2 and Phase 3 Studies
7/17/2017	[REDACTED]-srpt-email-ack-request-[REDACTED]-53-study-status-53.pdf	IND 119982	Sarepta acknowledgment of receipt - Information Request - Status of Ongoing Phase 2 and Phase 3 Studies
7/17/2017	[REDACTED]-srpt-email-ack-request-[REDACTED]-53-study-status.pdf	[REDACTED];#IND 119982	Sarepta acknowledgment of receipt - Information Request - Status of Ongoing Phase 2 and Phase 3 Studies
7/17/2017	[REDACTED]-fda-email-request-[REDACTED]-53-study-status-51.pdf	[REDACTED];#IND 119982	FDA Information Request - Status of Ongoing Phase 2 and Phase 3 Studies
7/17/2017	[REDACTED]-fda-email-request-[REDACTED]-53-study-status.pdf	[REDACTED];#IND 119982	FDA Information Request - Status of Ongoing Phase 2 and Phase 3 Studies
7/19/2017	[REDACTED]-sukl-letter [REDACTED]-ini-cta-add-questions-czech.pdf	[REDACTED];#IND 119982	Announcement of Grounds for Refusal of an Application for Notification of a Clinical Trial. [REDACTED], Protocol number: [REDACTED], EudraCT number: 2015-002069-52. Agency requests amendment to both studies within 30 days to avoid refusal.

Date	Submission Activity Name	Application	Summary
10/29/2017	██████-srpt-email-fda-resp-fda-info-request-rec-171027.pdf	IND 119982	Email of the 1.11.1 response to FDA request received 10/27/17, with notice that the official response is being submitted later in the day on 10/30/17.
11/6/2017	██████-fda-email-ind119982-type-c-mtg-granted-proposed-new-date.pdf	IND 119982	FDA responded to our Nov. 1, 2017, Type B Meeting Request. The meeting was changed to a Type C meeting and the FDA proposed a new date and time.
11/8/2017	██████-srpt-email-fda-ind119982-accept-type-c-mtg-proposed-dates.pdf	IND 119982	Sarepta replied in agreement to FDA's Type C meeting date proposal dated 11/7/17
11/13/2017	██████-fda-email-courtesy-copy-type-c-meeting-granted.pdf	IND 119982	FDA sent a courtesy copy of the letter granting a Type C Meeting for 1/24/18
11/13/2017	██████-srpt-email-fda-request-new-delivery-date-briefing-doc.pdf	IND 119982	Sarepta reached out to FDA to request more time to prepare the Type C Briefing Book for the 1/24/18 meeting
11/13/2017	██████-fda-letter-ind119982-type-c-meeting-granted.pdf	IND 119982	FDA letter granting Type C Meeting on January 24 2018. (Note: a request to change the date was later sent and this meeting was rescheduled for February 6, 2018)
11/14/2017	██████-fda-email-response-request-new-delivery-date-briefing-doc.pdf	IND 119982	FDA's response regarding Sarepta's request for an additional week to deliver the Type C Briefing Book for the 1/24/18 meeting
11/27/2017	██████-fda-letter-4053-type-c-granted.pdf	IND 119982	4053 Type C Meeting, Feb 6, 2018
11/28/2017	██████-fda-email-type-c-mtg-granted-letter.pdf	IND 119982	FDA sent email with attachment of Meeting Granted Letter for Type C Meeting on 2/6/18
12/18/2017	██████-srpt-email-fda-courtesy-copy-4053-bd.pdf	IND 119982	Sarepta sent courtesy copy of 4053 Briefing Document for 2/6/18 Type C Meeting
12/19/2017	██████-fda-email-thanks-courtesy-copy-type-c-briefing-book.pdf	IND 119982	FDA sent thank you for the courtesy copy of the 2/6/18 Type C briefing document
1/21/2018	██████-srpt-email-fda-add-attendee-ind119982-type-c-mtg-06feb2018.pdf	IND 119982	Sarepta contacted FDA to provide a Foreign Visitor Form for the 06Feb2018, Type C Meeting for IND 119882
1/23/2018	██████-fda-email-acknowledge-receipt-add-attendee-for-visit-form-ind119982-type-c-mtg-06feb2018.pdf	IND 119982	FDA confirmed receipt of the Foreign Visitor Form for the 06Feb2018, Type C Meeting for IND 119882
1/25/2018	██████-fda-email-acknowledgement-breakthrough-therapy-request.pdf	IND 119982	FDA email copy of Acknowledgement Breakthrough Therapy Request letter
1/25/2018	██████-fda-letter-acknowledgement-breakthrough-therapy-request.pdf	IND 119982	FDA Acknowledgement Breakthrough Therapy Request letter
1/29/2018	██████-srpt-email-fda-new-sponsor-contact-██████-ind119982-██████.pdf	██████;IND 119982	New Sponsor Contact: Sarepta; ██████ & SRP-4053 Programs (IND 119982); ██████
1/29/2018	██████-fda-email-confirmation-receipt-new-contact-██████-██████.pdf	██████;IND 119982	FDA confirmation of receipt of new contact for ██████ and 4053

Date	Submission Activity Name	Application	Summary
	ind119982.pdf	119982	
1/31/2018	██████-fda-email-██████-4053-confirm-correspondence-received-contact-addition-██████.pdf	██████;#IND 119982	FDA confirmation of the addition of ██████ to IND 119982
1/31/2018	██████-fda-email-ind119982-type-c-mtg-prelim-comments.pdf	IND 119982	FDA preliminary comments for February 6, 2018 Type C Meeting
2/1/2018	██████-srpt-email-follow-up-fda-prelim-comments-type-c-mtg-06feb2018.pdf	IND 119982	Sarepta would like further discussion regarding questions 1, 2 and 4. We will aim to provide our slides on Monday evening, 5 February 2018. Provided an updated Sarepta attendee list for the meeting.
2/4/2018	██████-fda-email-confirm-receipt-sarepta-resp-fda-prelim-comments-06fe2018-type-c-mtg-ind119882.pdf	IND 119982	FDA confirming receipt of Sarepta's response to FDA Preliminary Comments for 06Feb2016 Type C Meeting
2/4/2018	██████-srpt-email-response-fda-prelim-comments-type-c-mtg-06feb18-ind119982.pdf	IND 119982	Sarepta response to FDA preliminary comments for 06Feb2018 Type C Meeting
2/6/2018	██████-fda-email-list-fda-attendees-06feb18-type-c-mtg-ind119882.pdf	IND 119982	FDA provided a list of FDA attendees for 06Feb2016 Type C Meeting
2/6/2018	██████-srpt-email-fda-thank-you-type-c-mtg-06-feb-18-ind119982-fda-attendee-list.pdf	IND 119982	Sarepta thank you to FDA for Type C meeting 06feb18 and for collaboration on this program, as well as the FDA attendee list provided 07feb2018
2/8/2018	██████-fda-email-rfi-██████-uk-stoppage.pdf	██████;#IND 119982	Reference is made to IND 119982 for golodirsén. We have the following request for information. We are aware that Study ██████ has been temporarily stopped in the UK due to a serious adverse event of rhabdomyolysis. Please provide additional information on the case and the reason that the study was halted. Specifically, please provide clarification on the UK specific stopping rules that caused the study to be halted. We request that you provide this information by COB February 12, 2018.
2/8/2018	██████-srpt-email-fda-confirm-receipt-rfi-██████-uk-stoppage.pdf	██████;#IND 119982	Sarepta confirmation of receipt of request from FDA regarding ██████ UK stoppage. Thank you for your email. We are in the process of preparing a communication for the Division and appropriate information sharing is occurring with the investigators.
2/14/2018	██████-srpt-email-fda-ind119982-sponsor-mtg-minutes-type-c-mtg-06feb18.pdf	IND 119982	Sarepta Sponser Meeting Minutes Type C Meeting with FDA 06Feb2018
2/21/2018	██████-fda-email-thanks-notify-type-b-mtg-request-to-be-	IND 119982	FDA thank you for notification of pending Type B Pre-NDA CMC

Date	Submission Activity Name	Application	Summary
	submitted-shortly.pdf		Meeting Request
2/21/2018	██████-srpt-fda-email-notify-type-b-mtg-request-to-be-submitted-shortly.pdf	IND 119982	Sarepta notified FDA a Type B Pre-NDA CMC Meeting Request would be sent via gateway with in the next few days
2/26/2018	██████-fda-letter-4053-type-b-mtg-approved.pdf	IND 119982	FDA letter, Type B Pre-NDA CMC Meeting approved for May 3, 2018 12p - 1p, White Oak Building, Silver Spring Maryland
3/1/2018	██████-fda-letter-ind119982-type-c-mtg-minutes-06Feb18-meeting.pdf	IND 119982	FDA meeting minutes Type C meeting held on 06Feb2018
3/4/2018	██████-fda-email-type-c-mtg-minutes-06Feb18-meeting.pdf	IND 119982	FDA meeting minutes from 06Feb2018, Type C Meeting
3/19/2018	██████-email-fda-4053-btd-denied.pdf	IND 119982	Notice of denial of Breakthrough Designation
3/19/2018	██████-letter-fda-4053-btd-denied.pdf	IND 119982	Notice of denial of Breakthrough Designation
3/26/2018	██████-srpt-email-request-nda-number-4053.pdf	IND 119982	Email request to FDA for NDA number for 4053
3/28/2018	██████-fda-email-4053-nda-number-assigned.pdf	NDA 211970;#IND 119982	FDA assigned NDA number for 4053 Golodirsen
4/18/2018	██████-srpt-email-fda-ind119982-proposed-amendment-██████-essence-trial.pdf	IND 119982	Following our telephone conversations of Monday April 16th, AVI Biopharma International would like to make the Rapporteurs aware of a change in strategy with respect to the confirmatory study being proposed. This study is proposed as the means of addressing the Conditional Marketing Authorisation requirement to make comprehensive clinical data available.
4/19/2018	██████-fda-email-confirm-receipt-ind119982-proposed-amendment-██████-essence-trial-email.pdf	IND 119982-██████	Email to FDA with plan to modify ██████ protocol per the advice received in the 2/6/18 Type C Meeting.
4/23/2018	██████-fda-email-IND 119882-cmc-type-b-mtg-preliminary-responses.pdf	IND 119982	Sarepta response to FDA preliminary comments regarding Briefing Material for Type B CMC PreNDA Meeting
4/23/2018	██████-fda-letter-IND 119882-cmc-type-b-mtg-preliminary-responses.pdf	IND 119982	Official Letter: FDA preliminary comments regarding Briefing Material for Type B CMC PreNDA Meeting
4/23/2018	██████-srpt-email-fda-confirm-receipt-IND 119882-cmc-type-b-mtg-preliminary-responses.pdf	IND 119982	FDA confirms receipt of Sarepta response to FDA preliminary comments regarding Briefing Material for Type B CMC PreNDA Meeting
4/23/2018	██████-fda-email-ind119982-proposed-amendment-██████-essence-trial.pdf	IND 119982	Proposed Amendment to ██████ Protocol
5/1/2018	██████-fda-email-ind119882-preliminary-meeting-responses-pre-nda-cmc-mtg-cancelled.pdf	IND 119982	Email to notify the FDA of intent to send formal request to cancel Pre-NDA CMC Type B Meeting
5/1/2018	██████-fda-letter-ind119882-preliminary-meeting-responses-	IND 119982	FDA Letter confirming the cancellation Pre-NDA CMC Type B

Date	Submission Activity Name	Application	Summary
	pre-nda-cmc-mtg-cancelled.pdf		Meeting
5/14/2018	[REDACTED]-srpt-email-fda-ind119982-notice-type-c-mtg-request-proposed-amendment-trial.pdf	IND 119982; [REDACTED]	Notification to FDA regarding the submission a Type C Meeting to discuss FDA proposed changes to [REDACTED] trial
5/16/2018	[REDACTED]-fda-email-notification-type-c-mtg-request-received-essence [REDACTED] ind119982.pdf	[REDACTED];#IND 119982	FDA confirmation that the Type C meeting request was received and will be filed in both the [REDACTED] and the 119982 IND.
5/20/2018	[REDACTED]-srpt-email-fda-ind119982-seq0053-maintaining-integrity-following-safety-analysis [REDACTED].pdf	[REDACTED];#IND 119982	Follow up to a submission made to the golodirsen IND (SN0053) on 27 April 2018, request for comment [REDACTED] Safety Analysis
5/20/2018	[REDACTED]-fda-letter-ind119982-type-c-meeting-granted.pdf	[REDACTED];#IND 119982	Type C Meeting granted for 01Aug2018, 2-3pm. letter
5/20/2018	[REDACTED]-fda-email-ind119982-type-c-meeting-granted.pdf	[REDACTED];#IND 119982	Type C Meeting granted for 01Aug2018, 2-3pm. email
5/20/2018	[REDACTED]-fda-email-response-ind119982-seq0053-maintaining-integrity-following-safety-analysis [REDACTED].pdf	[REDACTED];#IND 119982	FDA confirmed receipt of Follow up email to a submission made to the golodirsen IND (SN0053) on 27 April 2018, request for comment [REDACTED] Safety Analysis
5/21/2018	[REDACTED]-fda-email-ind119982-fda-express-concern-maintaining-integrity-following-safety-analysis [REDACTED].pdf	[REDACTED];#IND 119982	FDA expressed concern regarding having too many people who have access to the unblinded data may lead to accidental information leaking. We recommend that most of the team members have access only to the unblinded analysis output, but not patient level data.
5/28/2018	[REDACTED]-srpt-email-fda-notice-contact-change-from [REDACTED].pdf	[REDACTED] IND 119982	Notice to FDA of Change in Regulatory Leadership from [REDACTED]
6/4/2018	[REDACTED]-fda-email-response-to-17may18-info-req-submission-response.pdf	IND 119982	The draft NDA TOC provided to FDA is missing validation report for RT-PCR. Acknowledge response to comment to confirm all image analysis with multiple pathologists.
6/4/2018	[REDACTED]-srpt-email-fda-acknowledgement-fda-response-to-17may18-info-req-submission-response.pdf	IND 119982	Confirming receipt of FDA feedback for 17May2018 info request
6/14/2018	[REDACTED]-fda-letter-ack-rolling-review-request-nda211970.pdf	IND 119982	FDA letter acknowledging SRPT request for rolling review on NDA 211970 for golodirsen
6/25/2018	[REDACTED]-fda-email-request-info-ind119982-image-file-format.pdf	IND 119982	Reference is made to your IND 119982 for golodirsen. We also refer to your submission of May 17, 2018, in response to the FDA minutes for the Feb 6, 2018, type C meeting. [REDACTED]

Date	Submission Activity Name	Application	Summary
			[REDACTED]
6/25/2018	[REDACTED]-srpt-email-fda-acknowledge-receipt-request-info-ind199882-image-file-format.pdf	IND 119982	SRPT acknowledges receipt of FDA email.
6/25/2018	[REDACTED]-fda-email-request-pre-nda-mtg-ind119882-granted.pdf	IND 119982	FDA acknowledging the SRPT meeting request and granting a date.
6/27/2018	[REDACTED]-srpt-email-fda-thanks-notification-request-pre-nda-mtg-ind119882-granted.pdf	IND 119982	SRPT acknowledges receipt of pre-NDA meeting granted letter
6/27/2018	[REDACTED]-fda-email-formal-letter-request-pre-nda-mtg-ind119882-granted.pdf	IND 119982	FDA grants pre-NDA meeting.
7/4/2018	[REDACTED]-fda-email-rfi-clinpharm-and-cardiac-safety.pdf	IND 119982	Reference is made to IND 119982 for golodirsen and to your 6/18/18 correspondence requesting a pre-NDA meeting. Please complete the attached ClinPharm and Cardiac Safety Table and include the response to this request in the meeting package. The meeting package is due to the Agency by 8/10/18.
7/4/2018	[REDACTED]-srpt-email-confirm-rec-rfi-clinpharm-and-cardiac-safety.pdf	IND 119982	I confirm receipt.
7/5/2018	[REDACTED]-srpt-email-foreign-visitor-data-form [REDACTED].pdf	IND 119982	SRPT provided foreign visitor data form for [REDACTED] who will be present at FDA pre-NDA Meeting
7/5/2018	[REDACTED]-fda-email-confirming-receipt-foreign-visitor-data-form [REDACTED].pdf	IND 119982	FDA confirmed receipt of Foreign Visitor Data Form for [REDACTED] who will be present at FDA for pre-NDA meeting for golodirsen.
7/18/2018	[REDACTED]-fda-email-4053-nda211970-fda-request-for-study-data.pdf	NDA 211970	FDA's preference on what information they want provided in a dataset and how to receive that data
7/18/2018	[REDACTED]-srpt-email-fda-4053-nda211970-response-to-rfi-for-study data.pdf	NDA 211970	Sarepta's confirmation that data will be provided by end of day
7/19/2018	[REDACTED]-srpt-email-45&53-list-sarepta-attendees-typec-meeting-august 1st.pdf	IND 119982	Type C Meeting Request (updated list of Sarepta attendees for the August 1st meeting)

Date	Submission Activity Name	Application	Summary
7/23/2018	██████-fda-email-missing-new-investigators-██████-ind119982.pdf	IND 119982	Missing 1572s in ██████
7/23/2018	██████-fda-email-4053-nda-rolling-review-acceptance.pdf	NDA 211970;#IND 119982	Your proposal for the timeline and content of the rolling submission is acceptable
7/23/2018	██████-srpt-email-response-missing-investigators-██████-ind119982.pdf	██████;#IND 119982	Response sent to FDA about the missing NI
7/24/2018	██████-fda-email-██████-ind-119982-sn0053-trial-integrity-memo-safety-analysis.pdf	IND 119982	FDA confirming receipt of response
7/24/2018	██████-srpt-email-██████-ind-119982-sn-0053-maintaining-integrity-following-safety-analysis-essence-memo-attached.pdf	IND 119982	maintaining the integrity following safety analysis for ESSENCE - with the memo's attached
7/24/2018	██████-srpt-email-4053-ind119982-response-comments-sn0059.pdf	IND 119982	IND 119982 golodirsen (response to comments related to May 17, 2018 submission SN0059)
7/25/2018	██████-fda-email-4053-ind119982-req-telecon-comments-sn0059.pdf	IND 119982	FDA providing a telecon timeslot to discuss on the responses
7/25/2018	██████-srpt-email-4053-ind119982-accept-telecon-response-sn0059.pdf	IND 119982	SRPT accepting the telecon
7/26/2018	██████-fda-email-scheduled-visit-notification-from.pdf	IND 119982	Scheduled Visit Notification from
7/26/2018	██████-fda-letter-1aug-type-c-mtg-prelim-comments.pdf	██████;#IND 119982	Preliminary meeting comments for Type C Meeting (1 August 2018)
7/30/2018	██████-fda-email-4053-nda211970-telecon-180731-meeting-minutes.pdf	NDA 211970	Teleconference to propose ██████
8/2/2018	██████-srpt-email-fda-ind119882-follow-up-██████-type-c-mtg.pdf	IND 119982; ██████	
8/5/2018	██████-fda-email-ind119882-follow-up-██████-type-c-mtg-thanks-sent-response-with-submission-proposed-analysis.pdf	IND 119982	
8/9/2018	██████-srpt-email-nda211970-response-consent-submit-svs-filetype-ectd.pdf	NDA 211970	FDA ESG response granting permission to request for permission to submit .svs files
8/9/2018	180810-fda-email-nda211970-consent-submit-svs-filetype-ectd.pdf	NDA 211970	SRPT request to submit .svs files
8/22/2018	██████-srpt-email-4053-ind119982-acknowledging-receipt-meeting-minutes-aug1st.pdf	IND 119982	Confirmed receipt of meeting minutes email.
8/22/2018	██████-fda-email-4053-ind119982-type-c-meeting-mins.pdf	██████;#IND 119982	FDA Type C Meeting Minutes for August 1, 2018 Meeting to discuss ESSENCE Protocol ██████
8/26/2018	██████-srpt-email-4053-ind119982-correction-errors-briefing-package.pdf	IND 119982	Informed FDA of corrections to typographical error ██████

Date	Submission Activity Name	Application	Summary
			[REDACTED]
8/29/2018	[REDACTED]-srpt-email-4053-ind119982-requesting response-sn0071.pdf	IND 119982	SRPT request receipt of response from Division regarding submission SN0071 (Submitted on 17 Aug 2018)
8/29/2018	[REDACTED]-fda-email-4053-ind119982-response-requesting response-sn0071.pdf	IND 119982	Acknowledge receipt of email
8/30/2018	[REDACTED]-srpt-email-4053-ind119982-pre-nda-meeting-sarepta-attendees.pdf	IND 119982	SRPT provide FDA list of attendees and titles
9/3/2018	[REDACTED]-fda-email-4053-ind119982-acknowledgment-correction-errors-briefing-package.pdf	IND 119982	FDA acknowledging receipt of the correctional errors in the briefing package.
9/3/2018	[REDACTED]-srpt-email-4053-nda211970-acknowledgment-image-files-sent-sn0071-ind119982.pdf	NDA 211970	SRPT acknowledging the image files were sent in SN 0071.
9/3/2018	[REDACTED]-fda-email-4053-ind119982-ir-status-assay-anti-golodirsen-antibody.pdf	IND 119982	FDA requesting information regarding the status of the Assay of Antibodies for Golodirsen.
9/3/2018	[REDACTED]-fda-email-4053-nda211970-image-files-sent-sn0071-ind119982.pdf	NDA 211970	FDA requesting information regarding the status of the Image files sent in Sn 0071.
9/4/2018	[REDACTED]-srpt-email-4053-ind119982-ir-response-status-assay-anti-golodirsen-antibody.pdf	IND 119982	SRPT Emailing FDA the response document with the status of the assay for the Anti Golodirsen Antibody.
9/4/2018	[REDACTED]-srpt-email-4053-nda-211970-pre-nda-meeting-invitation-queries.pdf	NDA 211970	SRPT Emailing FDA about questions regarding the meeting invitations.
9/4/2018	[REDACTED]-fda-email-4053-ind119982-ir-acknowledge-status-assay-anti-golodirsen-antibody.pdf	IND 119982	FDA acknowledging the response for the information request.
9/5/2018	[REDACTED]-srpt-email-4053-nda211970-passcode-bioassay-image-external-drive.pdf	NDA 211970	SRPT email with the passcode for the bioassay image external drive for Archives.
9/5/2018	[REDACTED]-srpt-email-4053-nda211970-response-image-files-sent-sn0071-ind119982.pdf	NDA 211970	SRPT Emailing to FDA about the response with the tiff image files sent in SN 0071.
9/6/2018	[REDACTED]-srpt-email-4053-nda-211970-pre-nda-meeting-follow-up-invitation-queries.pdf	NDA 211970	SRPT Emailing FDA questions about the Invitations for the Pre-NDA meeting.
9/6/2018	[REDACTED]-fda-email-4053-ind119982-acknowledgment-ir-response-status-assay-anti-golodirsen-antibody.pdf	IND 119982	FDA Emailing SRPT with acknowledgment of receipt of the Information Request Response Submission.
9/6/2018	[REDACTED]-fda-email-4053-nda-211970-acknowledgment-pre-nda-meeting-follow-up-invitation-queries.pdf	NDA 211970	FDA acknowledging the questions regarding the Pre-NDA meeting invitations.
9/6/2018	[REDACTED]-fda-email-4053-ind119982-pre-meeting-prelim-comments.pdf	IND 119982	FDA providing SRPT with the preliminary responses for the questions.
9/6/2018	[REDACTED]-fda-email-4053-ind119982-pre-nda-mtg-status-prelim-comm.pdf	IND 119982	FDA targeting to provide the preliminary comments today and Response regarding the QR codes.

Date	Submission Activity Name	Application	Summary
9/9/2018	[REDACTED]-srpt-email-4053-nda-211970-acknowledgment-invitation-queries-response.pdf	NDA 211970	SRPT emailing FDA with the acknowledgment of the response to the meeting invitation questions.
9/9/2018	[REDACTED]-srpt-email-4053-ind119982-prelim-comments-discussion.pdf	IND 119982	Based on the Prelim Comments SRPT would like to discuss questions 1, 2 and 5 and no discussion regarding other questions are needed.
9/9/2018	[REDACTED]-fda-email-4053-ind119982-acknowledgment-type-b-pre-nda-meeting-questions.pdf	IND 119982	FDA acknowledging receipt of the email and the barcode attachment.
9/9/2018	[REDACTED]-srpt-email-4053-ind119982-follow-up-questions-type-b-pre-nda-meeting-questions.pdf	IND 119982	SRPT emailing FDA to understand what "Discussion of the Content of a Complete Application" would mean.
9/9/2018	[REDACTED]-srpt-email-4053-ind119982-acknowledgment-participants-qr-codes.pdf	IND 119982	SRPT acknowledging FDA's confirmation that all 10 Sarepta meeting attendees are accounted for in the FDA visitor system
9/13/2018	[REDACTED]-fda-letter-n211970-ack-presub.pdf	NDA 211970	Acknowledgement of receipt of Part 1 of rolling NDA
10/1/2018	[REDACTED]-srpt-email-4053-ind119982-expedited-review-sample-iss-datasets.pdf	IND 119982	SRPT submitted sample ISS datasets and data definition files IND 119982, Sequence 0075
10/9/2018	[REDACTED]-fda-letter-ind119982-pre-nda-meeting-minutes.pdf	IND 119982	Copy of official meeting minutes from Sept. 11, 2018 to discuss format and content of NDA for SRP-4053.
10/10/2018	[REDACTED]-fda-email-4053-ind119982-sample-iss-datasets-data-definition.pdf	IND 119982	FDA responding to SRPTs email dtd 2nd Oct that they have included our comments regarding the sample ISS datasets and data definition files as post-meeting notes undet Q2 in Pre-NDA meeting minutes.
10/10/2018	[REDACTED]-srpt-email-4053-ind119982-sample-iss-datasets-data-definition.pdf	IND 119982	SRPT thanking FDA for the response.
10/16/2018	[REDACTED]-fda-email-4053-nda211970-ir-cor-ndair-01.pdf	NDA 211970	Information request for NDA 211070 for Golodirsen injection.
11/1/2018	[REDACTED]-fda-email-4053-nda211970-ir-cmc-(cor-ndair-01).pdf	NDA 211970	Please refer to your New Drug Application (NDA) dated August 27, 2018, received August 27, 2018, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Golodirsén Injection. We are reviewing the CMC section(s) of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA by Friday, November 9, 2018. [REDACTED]

Date	Submission Activity Name	Application	Summary
12/4/2018	-srpt-email-4053-nda211970-external-usb-drive-data.pdf	NDA 211970	Sarepta plans to submit the final NDA Sequence in December 2018 and it will be accompanied by a USB Drive containing all requested raw image files (90GB).
12/5/2018	-srpt-email-4053-sarepta-contact-change.pdf	NDA 211970	SRPT inform FDA of contact change after departure.
12/6/2018	-srpt-email-4053-nda211970-external-usb-drive-data.pdf	NDA 211970	SRPT inform FDA targeting submission of the final portion of the NDA during the week of 17Dec2018.
12/6/2018	-fda-email-4053-nda211970-external-usb-drive-data.pdf	NDA 211970	FDA requests anticipated date for submission of the final portion of the NDA.
12/18/2018	-fda-email-4053-nda211970-cmc-ir.pdf	NDA 211970	We request a prompt written response in order to continue our evaluation of your NDA by Friday, January 4, 2019. 1. Please provide hold time data for the bulk drug product solution prior to filling. 2. Provide leachables/extractables and compatibility study data for the drug product solution with LevMixer bag.
12/18/2018	-srpt-email-4053-nda211970-ack-cmc-ir.pdf	NDA 211970	FDA Acknowledging to be the Point of CONTACT for all Future Conversations
12/18/2018	-fda-email-4053-nda211970-ack-grl-change-cmc-ir.pdf	NDA 211970	Sarepta acknowledgement of Golodersin NDA 211970 CMC RFI received 19Dec2018
12/18/2018	-srpt-email-fda-notice-shipment-nda-211970-external-hard-drive-for-sq.0004-rolling-nda-pt2.pdf	NDA 211970	SRPT Informing FDA about The USB Drive (external to the eCTD portion of NDA 211970 SQ0004) containing all requested image files
12/18/2018	-srpt-email-fda-notice-nda211970-rolling-part2-submission-sent-through-esg.pdf	NDA 211970	SRPT Emailing FDA to Inform them of the ESG Transmission of Original NDA Rolling Submission Part 2 has begun.
1/2/2019	-fda-letter-4053-nda211970-nda-acknowledgement.pdf	NDA 211970	NDA Acknowledgement Letter. PDUFA Date: 17 February 2019
1/3/2019	-fda-email-4053-nda211970-info-req-follow-up.pdf	NDA 211970	FDA Following Up on the CMC IR recvd 181219
1/3/2019	-srpt-email-4053-nda211970-ack-resp-info-req-follow-up.pdf	NDA 211970	SRPT Acknowledging that the Response for the CMC IR recvd 181219 Would be Submitted on 190104

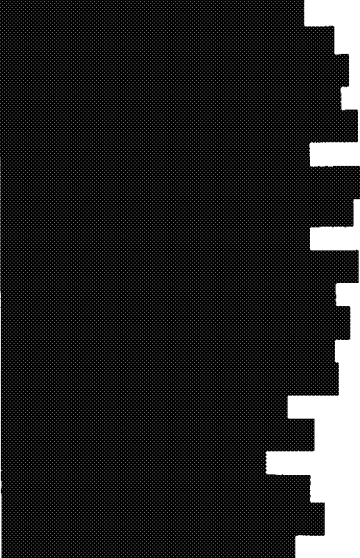
Date	Submission Activity Name	Application	Summary
1/4/2019	[REDACTED]-fda-email-4053-nda211970-rfi-timing-ecg-collection.pdf	NDA 211970	Reference is made to your new drug application (NDA) 211970 for golodirsen submitted on December 19, 2018. We request the following information by February 8, 2019. Please clarify the timing of ECG collection relative to dosing for the ECG assessments described in Table 1 in the "Summary of Clinical Safety".
1/4/2019	[REDACTED]-srpt-email-fda-4053-nda211970-ack-rfi-timing-ecg-collection.pdf	NDA 211970	SRPT confirmed receipt of FDA asked to clarify timing of ECG collection relative to dosing for the ECG assessments described in Table 1 in the "Summary of Clinical Safety". I confirm receipt.
1/10/2019	[REDACTED]-fda-email-nda211970-ack-120-day-immunogenicity-report.pdf	NDA 211970	
1/10/2019	[REDACTED]-srpt-email-fda-nda211970-120-day-immunogenicity-report.pdf	NDA 211970	
1/13/2019	[REDACTED]-fda-email-nda211970-cmc-ir.pdf	NDA 211970	<p>Please refer to your New Drug Application (NDA) dated August 27, 2018, received August 27, 2018, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Golodirsen Injection. We are reviewing the CMC section(s) of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA by Friday, January 18, 2019. 1.</p> <p>[REDACTED]</p>

Date	Submission Activity Name	Application	Summary
			[REDACTED]
1/13/2019	[REDACTED]-srpt-email-fda-nda211970-ack-cmc-ir.pdf	NDA 211970	Sarepta confirms receipt of CMC RFI received January 14, 2019 consisting of 6 questions. I confirm receipt of your information request.
1/14/2019	[REDACTED]-srpt-email-fda-updated-list-personnel-authorized-comm-fda.pdf	[REDACTED] IND 119982 [REDACTED] NDA 211970	Acknowledgement of Sarepta email providing an updated list of personnel
1/14/2019	[REDACTED]-fda-email-ack-updated-list-personnel-authorized-comm-fda.pdf	[REDACTED] IND 119982 [REDACTED] NDA 211970	FDA acknowledgement of Sarepta email providing an updated list of personnel authorized to communicate with FDA. Ask Sarepta to formally submit to each application.

Date	Submission Activity Name	Application	Summary
1/14/2019	██████████-srpt-email-fda-ack-updated-list-personnel-authorized-comm-fda.pdf	██████████ IND 119982 ██████████ NDA 211970	Sarepta replied to FDA acknowledgement of Sarepta email providing an updated list of personnel and confirmed that a formal submission would be made to each application.
1/25/2019	██████████-fda-email-nda211970-resp-120-day-immunogenicity-report.pdf	NDA 211970	FDA finds proposed plan acceptable to initiate golodirsen Study 4053-101 ██████████ ██████████
1/25/2019	██████████-srpt-email-fda-nda211970-advice-120-day-immunogenicity-report.pdf	NDA 211970	proposed plan to initiate golodirsen Study 4053-101 ██████████ ██████████
1/28/2019	██████████-fda-email-4053-nda211970-igg-status-120-day-immunogenicity-report.pdf	NDA 211970	FDA request an update on the status of ██████████
1/28/2019	██████████-srpt-fda-email-4053-nda211970-igg-status-120-day-immunogenicity-report.pdf	NDA 211970	SRPT confirm the ██████████ ██████████ has been submitted, reviewed and approved by FDA as part of ██████████. Plan to submit the ██████████ ██████████ this week and the ██████████ in Feb.
1/29/2019	██████████-fda-email-4053-nda211970-rfi-cr-cle-study.pdf	NDA 211970	Please refer to your new drug application (NDA) 211970 for golodirsen submitted on December 19, 2018. We request the following information by February 6, 2019. To facilitate the review of the study report SR-18-090 (CR-CLE Study number: 180921.TBX), please submit the following information for each experiment: a. Raw and unaltered electrophysiology records (e.g., no baseline subtraction or zero'ing of baseline). The file format for the raw electrophysiology records should be in xls, xlsx or xpt format, and contain at a minimum information about time, voltage and current signals (note specific units for these signals). b. An overview file, e.g. in xls, xlsx, xpt or txt, describing the experimental conditions for each of the raw electrophysiology records. The description should include at a minimum the name of the file, temperature of the recording, when drugs and at what concentrations were added, and other information relevant to interpret the results.
1/29/2019	██████████-srpt-email-fda-4053-nda211970-ige-status-120-day-immunogenicity-report.pdf	NDA 211970	SRPT confirm the ██████████ ██████████ was submitted to ██████████

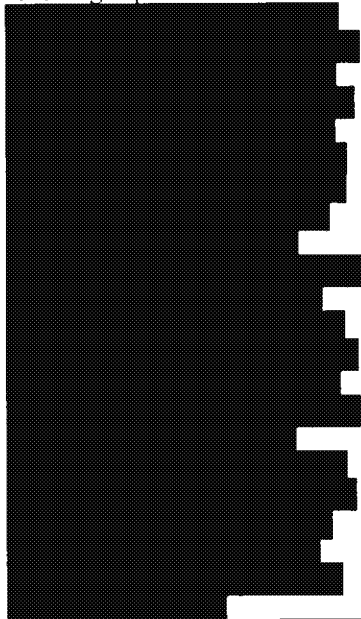
Date	Submission Activity Name	Application	Summary
			28Jan2019
1/29/2019	██████-srpt-email-fda-4053-nda211970-rfi-ack-western-blot-test-facility.pdf	NDA 211970	SRPT confirm receipt of FDA request for clarity on the multiple facilities listed for western blot study. I confirm receipt of your email.
1/29/2019	██████-srpt-email-fda-4053-nda211970-rfi-ack-cr-cle-study.pdf	NDA 211970	SRPT confirm receipt of FDA request for information re: NDA211970/CR-CLE Study
1/29/2019	██████-fda-email-4053-nda211970-rfi-western-blot-test-facility.pdf	NDA 211970	Please refer to your new drug application (NDA) 211970 for golodirsén submitted on December 19, 2018. We have the following request for information. In study report SR-17-044, you list multiple facilities that were involved in the western blot study. You state that the western blot immunodetection method was carried out in a controlled laboratory setting at ██████████ We are unclear on whether your laboratories are based in this location. Please clarify if this location houses the laboratories where the western blot immunodetection was carried out, and where the analysts and raw data records related to the study report SR-17-044 are located. Provide this information by COB January 30, 2019.
1/30/2019	██████-fda-email-4053-nda211970-120-day-immunogenicity-report.pdf	NDA 211970	FDA not able to advise on the timing of the initiation of golodirsén study 4053-101 ██████████ sample testing.
1/31/2019	██████-fda-letter-4053-nda211970-proprietary-name-acknowledgment.pdf	NDA 211970	FDA proprietary name acknowledgement for ██████████
2/6/2019	██████-fda-email-4053-nda211970-rfi-clinical-sites-enrolled-icf.pdf	NDA 211970	Reference is made to your new drug application (NDA) 211970 for golodirsén submitted on December 19, 2018. We ask that you provide a response to the following request by COB, Friday, 2/8/2019. Please provide the number of subjects currently enrolled in Protocol ██████████ for Sites 401 and 403. Please submit Informed Consent Documents for Protocols 4053-101 and ██████████. If these have been submitted with the NDA, please indicate the location in the submission.
2/6/2019	██████-srpt-email-fda-4053-nda211970-ack-rfi-clinical-sites-enrolled-icf.pdf	NDA 211970	I confirm receipt of your email.

Date	Submission Activity Name	Application	Summary
2/11/2019	██████-fda-email-4053-nda211970-rfi-monitoring-reports-france.pdf	NDA 211970	Reference is made to your new drug application (NDA) 211970 for golodirsen submitted on December 19, 2018. We have the following request for information. Submit the monitoring reports for Sites 401 and 403 for Protocols 4053-101 and ██████. For Site 403, located in France, if monitoring reports are available in English, please submit the English version. Please submit by COB, Tuesday, 2/19/2019.
2/11/2019	██████-srpt-email-fda-4053-nda211970-ack-rfi-monitoring-reports-france.pdf	NDA 211970	SRPT confirms receipt of FDA request for information on monitoring report for sites 401 and 403 for protocols 4053-101 and ██████. I confirm receipt of your email.
2/12/2019	██████-srpt-email-fda-4053-nda211970-ack-translators-servais-france.pdf	NDA 211970	SRPT confirm receipt of email.
2/12/2019	██████-fda-email-4053-nda211970-translators-██████-france.pdf	NDA 211970	FDA request assistance with translators for ██████ site.
2/12/2019	██████-srpt-email-fda-4053-nda211970-questions-translators-██████-france.pdf	NDA 211970	SPRT asks FDA to clarify which two investigators they are referring to. ██████ is the principle investigator for both Study 4053-101 and study ██████
2/12/2019	██████-fda-email-4053-nda211970-clarification-translators-██████-france.pdf	NDA 211970	SRPT refer two USFDA investigators. ██████ is the principle investigator for both Study 4053-101 and study ██████
2/13/2019	██████-fda-email-4053-nda211970-nda-filing-communication.pdf	NDA 211970	FDA provide courtesy copy of FDA filing communication.
2/13/2019	██████-fda-letter-4053-nda211970-nda-filing-communication.pdf	NDA 211970	FDA provide hard copy of FDA filing communication.
2/13/2019	██████-srpt-email-fda-4053-nda211970-ack-nda-filing-communication.pdf	NDA 211970	SRPT confirm receipt of email of FDA provide hard copy of FDA filing communication.
2/26/2019	██████-srpt-email-fda-4053-nda211970-immunogenicity-deferral.pdf	NDA 211970	SRPT sponsor proposed changes to NDA section 1.12, requesting immunogenicity study deferral. Plan to separately submit a new 1.11.3 document which will cross reference the submission of ██████ to the ██████ since these methods will be applicable to both compounds.
2/27/2019	██████-fda-email-4053-nda211970-midcycle-communication-190403.pdf	NDA 211970	FDA tentatively schedule MCC tcon 11 April 2019
2/27/2019	██████-srpt-email-fda-4053-nda211970-updated-cmc-information.pdf	NDA 211970	SRPT plans to update NDA with CMC information of leachables results.
2/27/2019	██████-srpt-email-fda-4053-nda211970-ack-rmidcycle-	NDA 211970	SRPT confirm receipt and tentatively scheduled MCC tcon

Date	Submission Activity Name	Application	Summary
	communication-190411.pdf		date.
2/27/2019	██████-fda-email-4053-nda211970-response-immunogenicity-deferral.pdf	NDA 211970	FDA provide information to provide in cross reference document for NDA 211970
2/27/2019	██████-srpt-email-fda-4053-nda211970-ack-response-immunogenicity-deferral.pdf	NDA 211970	SRPT thanks for guidance on submitting cross reference document for NDA 211970
3/1/2019	██████-srpt-email-fda-4053-nda211970-acceptance-rmidcycle-communication-190411.pdf	NDA 211970	SRPT confirm tentatively scheduled MCC tcon on 11April2019 is acceptable.
3/3/2019	██████-fda-email-4053-nda211970-ack-updated-cmc-information.pdf	NDA 211970	FDA confirms receipt of email regarding updating CMC information for NDA211970
3/3/2019	██████-srpt-email-fda-4053-nda211970-confirm-updated-cmc-information.pdf	NDA 211970	SRPT requests FDA confirmation of support in making updates to submission to CMC information in NDA 211970 at this stage of the NDA review.
3/4/2019	██████-srpt-email-fda-4053-nda211970-thank-updated-cmc-information.pdf	NDA 211970	SRPT thank for the follow up and inform FDA submission of updated CMC information in NDA 211970 will be made later in the week.
3/4/2019	██████-fda-email-4053-nda211970-ack-updated-cmc-information.pdf	NDA 211970	FDA will consult team regarding making updates to submission to CMC information in NDA 211970 at this stage in the game.
3/4/2019	██████-fda-email-4053-nda211970-confirmation-updated-cmc-information.pdf	NDA 211970	FDA confirms support in making updates to submission to CMC information in NDA 211970 at this stage of the NDA review.
3/4/2019	██████-fda-email-4053-nda211970-thank-updated-cmc-information.pdf	NDA 211970	FDA thank you for SRPT notifying that updated CMC information in NDA 211970 submission will be made later in the week.
3/11/2019	██████-fda-letter-4053-nda211970-rfi-method-verification.pdf	NDA 211970	Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Golodirsén Injection, 50mg/mL. 

Date	Submission Activity Name	Application	Summary
			[REDACTED]
3/11/2019	[REDACTED]-fda-email-4053-nda211970-rfi-ack-method-verification.pdf	NDA 211970	FDA acknowledge email of method verification request; FDA requests confirmation request of materials was received and ETA on ship date.
3/11/2019	[REDACTED]-srpt-email-fda-nda211970-rfi-ack-method-verification.pdf	NDA 211970	I confirm receipt and will get back to you with a shipping estimate.
3/15/2019	[REDACTED]-srpt-email-fda-4053-nda211970-rfi-response-method-verification.pdf	NDA 211970	Sarepta is in process of securing the materials and documents FDA has requested. [REDACTED]

Date	Submission Activity Name	Application	Summary
3/18/2019	[REDACTED]-fda-email-4053-nda211970-ack-response-method-verification.pdf	NDA 211970	FDA confirm receipt of SRPT materials and request package be sent when available.
3/25/2019	[REDACTED]-fda-email-4053-nda211970-proprietary-name.pdf	NDA 211970	FDA provide decision letter for proposed proprietary name submission under NDA 211970 (golodirsen)
3/25/2019	[REDACTED]-fda-letter-4053-nda211970-proprietary-name.pdf	NDA 211970	FDA provide decision letter for proposed proprietary name submission under NDA 211970 (golodirsen)
3/25/2019	[REDACTED]-srpt-email-fda-4053-nda211970-ack-proprietary-name.pdf	NDA 211970	SRPT acknowledge receipt of FDA decision letter for proposed proprietary name submission under NDA 211970 (golodirsen)
3/26/2019	[REDACTED]-fda-email-4053-nda211970-rfi-western-blot.pdf	NDA 211970	Reference is made to your pending new drug application (NDA) 211970 for golodirsen submitted on December 19, 2018. We have the following request for information. Please provide responses by COB April 2, 2019. i [REDACTED]
3/26/2019	[REDACTED]-srpt-email-fda-4053-nda211970-ack-rfi-western-blot.pdf	NDA 211970	SRPT confirm receipt of request of information regarding pending new drug application (NDA) 211970
3/29/2019	[REDACTED]-fda-letter-4053-nda211970-prop-name-vyondys 53-sub-ack.pdf	NDA 211970	FDA acknowledge receipt of request for proposed proprietary name, Vyondys 53.
4/3/2019	[REDACTED] srpt-email-fda-4053-nda211970-method-verification-response.pdf	NDA 211970	SRPT informing FDA the method verification materials for NDA 211970 were shipped 03April2019.


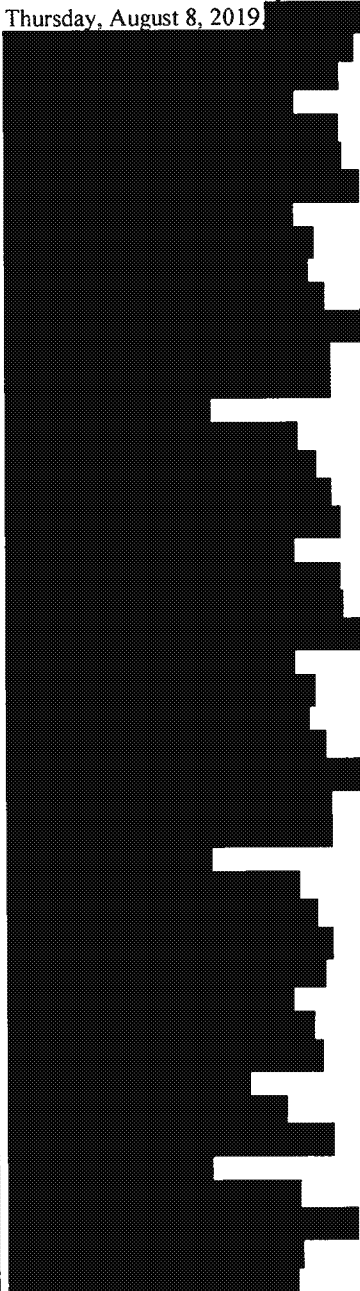
Date	Submission Activity Name	Application	Summary
4/3/2019	██████-fda-email-4053-nda211970-ack-response-rfi-method-verification.pdf	NDA 211970	FDA acknowledge of email regarding method verification materials for NDA 211970 were shipped 03April2019. Thank you very much for the update. I will send you a materials received letter.
4/4/2019	██████-srpt-email-fda-4053-nda211970-ack-comments-carton and container labeling.pdf	NDA 211970	SRPT confirm receipt of FDA comments to pending new drug application NDA 211970 for golodirsen carton and container labeling.
4/4/2019	██████-fda-email-4053-nda211970-comments-carton and container labeling.pdf	NDA 211970	FDA comments to pending new drug application NDA 211970 for golodirsen carton and container labeling.
4/5/2019	██████-fda-email-4053-nda211970-ack-response-method-verification-materials-received.pdf	NDA 211970	FDA confirm receipt of Method Verification Materials received for NDA211970
4/5/2019	██████-fda-email-4053-nda211970-rfi-clinical-dystrophin-intensity-data.pdf	NDA 211970	Reference is made to your pending new drug application (NDA) 211970 for golodirsen submitted on December 19, 2018. We have the following request for information. 
4/5/2019	██████-srpt-email-fda-4053-nda211970-ack-rfi-clinical-dystrophin-intensity-data.pdf	NDA 211970	SRPT confirm receipt of FDA request for information re: NDA211970 for golodirsen on dystrophin intensity data. I confirm receipt of your email.
4/5/2019	██████-fda-letter-4053-nda211970-ack-response-method-verification-materials-received.pdf	NDA 211970	FDA confirm receipt of Method Verification Materials received for NDA211970
4/9/2019	██████-srpt-email-fda-4053-nda211970-midcycle-communication.pdf	NDA 211970	SRPT request FDA agenda for Midcycle Communication tcon.
4/9/2019	██████-fda-email-4053-nda211970-midcycle-communication-agenda.pdf	NDA 211970	FDA inform SRPT the Midcycle communication (MCC) is intended to provide an update on the status of

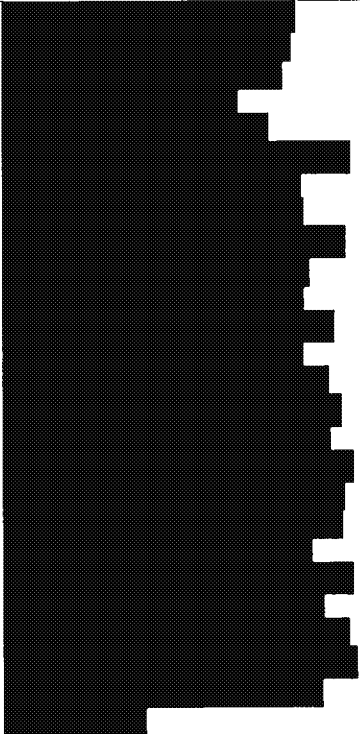








Date	Submission Activity Name	Application	Summary
			the review of application. Anticipate to end MCC agenda later today.
4/10/2019	██████-fda-letter-4053-nda211970-mcc-agenda.pdf	NDA 211970	FDA provide meeting agenda and list of participants for Midcycle Communication tcon on 11April2019.
4/10/2019	██████-fda-email-4053-nda211970-mcc-agenda.pdf	NDA 211970	FDA provide meeting agenda and list of participants for Midcycle Communication tcon on 11April2019.
4/10/2019	██████-srpt-letter-fda-4053-nda211970-ack-mcc-agenda.pdf	NDA 211970	FDA confirm receipt of SRPT participants Mid-Cycle communication tcon.
4/11/2019	██████-srpt-letter-fda-4053-nda211970-additional-attendees-mcc.pdf	NDA 211970	SRPT provides additional participants to Mid-Cycle Communications tcon.
4/11/2019	██████-srpt-email-fda-4053-nda211970-ack-rfi-clinical-narrative-summary.pdf	NDA 211970	SRPT confirms receipt of FDA request for information regarding NDA 211970 referring to listing Table 16.2.2. I confirm receipt.
4/11/2019	██████-fda-email-4053-nda211970-rfi-clinical-narrative-summary.pdf	NDA 211970	Reference is made to your pending NDA 211970 for golodirsén submitted on December 19, 2018. We have the following request for information. Referring to your Listing Table 16.2.2, provide a written narrative summary about the details surrounding each occasion of violations or deviations of unblinding, enrollment in violation of inclusion/exclusion criteria, and incorrect dose or infusion method. Please provide your response in 3 business days.
4/11/2019	██████-srpt-email-fda-4053-nda211970-mcc-additinal-attendee.pdf	NDA 211970	SRPT inform FDA of additional participant on regarding NDA 211970 mid-cycle communication
4/19/2019	██████-srpt-email-fda-4053-nda211970-follow-up-inspection-coa.pdf	NDA 211970	SRPT inform FDA plan to change practices to have CofAs stored locally, rather than on manufacturer website. Will send fourth and final CofA once received from vendor.
4/19/2019	██████-fda-email-4053-nda211970-ack-follow-up-inspection-coa.pdf	NDA 211970	FDA request confirmation when SRPT receives 4th COA printout
4/23/2019	██████-srpt-email-fda-4053-nda211970-follow-up-inspection-last-coa.pdf	NDA 211970	SRPT provides 4th and final CofA to FDA
5/3/2019	██████-fda-letter-4053-nda211970-mcc-fda-meeting-minutes.pdf	NDA 211970	FDA mid-cycle communicate meeting minutes for NDA 211970 on 11Apr2019
5/3/2019	██████-fda-email-4053-nda211970-mcc-fda-meeting-minutes.pdf	NDA 211970	FDA provided meeting minutes for mid-cycle commuication tcon re: golodirsén NDA 211970. Since IND 77429 is being cross referenced in the golodirsén application, IND 77429 should be listed under the cross references section of 356h Form

Date	Submission Activity Name	Application	Summary
5/3/2019	██████-srpt-email-fda-4053-nda211970-ack-mcc-fda-meeting-minutes.pdf	NDA 211970	SRPT acknowledge receipt of FDA provided meeting minutes for mid-cycle communication tcon re: golodirsen NDA 211970. Since IND 77429 is being cross referenced in the golodirsen application, IND 77429 should be listed under the cross references section of 356h Form
5/6/2019	██████-fda-email-4053-nda211970-rfi-clinical-pharmacology.pdf	NDA 211970	Reference is made to your new drug application (NDA) 211970 for golodirsen submitted on December 19, 2018. We have the following request for information. We ask for a response by COB, Friday 5/10/19. Regarding NDA 211970, please complete the bioanalytical method performance as explained in the attached document and it's performance in study (4053-101).
5/6/2019	██████-srpt-email-fda-4053-nda211970-ack-rfi-clinical-pharmacology.pdf	NDA 211970	SRPT confirm receipt of FDA request for information regarding NDA 211970 for complete bioanalytical method performance and performance in study (4053-101). I confirm receipt.
5/9/2019	██████-fda-email-4053-nda211970-rfi-clinical-proteinuria.pdf	NDA 211970	Reference is made to your new drug application (NDA) 211970 for golodirsen submitted on December 19, 2018. We have the following request for information. Provide this information by COB, Monday 5/13/19. For all subjects with an AE of proteinuria, regardless of treatment, provide a narrative including entry lab values and relevant (renal) medical history, and conmeds. Include progression through the trial(s) on this issue particularly including any assessment of renal function, e.g., but not limited to quantitated protein.
5/9/2019	██████-srpt-email-fda-4053-nda211970-ack-rfi-clinical-proteinuria.pdf	NDA 211970	SRPT acknowledge receipt of FDA request for information re: NDA 211970 for all subjects with an AE of proteinuria. I confirm receipt of your request.
5/21/2019	██████-fda-email-4053-nda211970-late-cycle-meeting-request.pdf	NDA 211970	Confirmation of receipt of meeting request and meeting type
5/22/2019	██████-srpt-email-fda-4053-nda211970-request-for-telecon.pdf	NDA 211970	meeting type request for telecon or face to face option
5/22/2019	██████-fda-email-4053-nda211970-advice-method-Identification.pdf	NDA 211970	confirmation Receipt of RFI and will follow-up
5/23/2019	██████-fda-email-4053-nda211970-rfi-study-info.pdf	NDA 211970	Confirmation of receipt of request for information
5/24/2019	██████-fda-email-4053-nda211970-rfi-iss-ekg-	NDA 211970	Confirmation of request for information

Date	Submission Activity Name	Application	Summary
	dataset.pdf		
5/29/2019	██████-fda-email-4053-nda211970-fda-meeting-acceptance.pdf	NDA 211970	FDA late-cycle meeting acceptance
5/29/2019	██████-srpt-email-fda-4053-nda211970-request-for-telecon.pdf	NDA 211970	Follow-up to meeting acceptance about telecon or face-to-face
5/31/2019	██████-fda-letter-4053-nda211970-proprietary-name-acceptable.pdf	NDA 211970	proprietary name acceptable letter received
5/31/2019	██████-fda-email-4053-nda211970-proprietary-name-acceptable.pdf	NDA 211970	proprietary name acceptable letter received
6/7/2019	██████-fda-email-4053-nda211970-rfi-study-fin-info.pdf	NDA 211970	Confirmation of receipt of information request
6/12/2019	██████-srpt-email-fda-4053-nda211970-proprietary-name-cond-approval.pdf	NDA 211970	proprietary name acceptable conditional approval letter received
6/17/2019	██████-srpt-email-fda-4053-nda211970-late-cycle-meeting-info.pdf	NDA 211970	late-cycle pre-meeting info such as dial in info, attendee list, and preliminary info
6/17/2019	██████-srpt-email-fda-4053-nda211970-late-cycle-meeting-info2.pdf	NDA 211970	response to out of office notification to first late-cycle pre-meeting info such as dial in info, attendee list, and preliminary info
6/20/2019	██████-fda-email-4053-nda211970-accelerated-approval.pdf	NDA 211970	accelerated approval notice that if received Sarepta plans to submit promotional materials and draft labeling
7/6/2019	██████-srpt-email-fda-4053-nda211970-meeting-package.pdf	NDA 211970	Sarepta confirming FDA meeting time and date, and also providing FDA with meeting background package for Late Cycle Meeting
7/11/2019	██████-fda-email-4053-nda211970-late-cycle-meeting-minutes.pdf	NDA 211970	FDA providing meeting minutes and feedback from Lat Cycle Meeting
7/17/2019	██████-srpt-email-fda-4053-nda211970-response-to-rfi.pdf	NDA 211970	Results from preliminary biometrics team discussion for Study ██████
7/17/2019	██████-fda-email-4053-nda211970-rfi-study-info.pdf	NDA 211970	I confirm receipt and will follow-up if there are questions.
7/23/2019	██████-fda-email-██████-4053-119982-██████-rfi-study-completion-date.pdf	IND 119982-██████	I confirm receipt.
7/24/2019	██████-srpt-email-fda-██████-4053-119982-██████-response-to-rfi-study-info.pdf	IND 119982-██████	Sarepta's response to RFI for enrollment status for Study ██████
7/24/2019	██████-srpt-email-fda-██████-4053-119982-██████-response-to-rfi-study-info2.pdf	IND 119982-██████	RFI for enrollment status for Study ██████
7/24/2019	██████-srpt-email-fda-██████-4053-119982-██████-response-to-rfi-study-info3.pdf	IND 119982-██████	RFI for enrollment status for Study ██████
7/25/2019	██████-fda-email-4053-nda211970-proposed-labeling-text.pdf	NDA 211970	Sarepta's confirmation of proposed labeling edits from Agency
7/29/2019	██████-fda-email-4053-nda211970-fda-labeling-comments.pdf	NDA 211970	FDA provides clarification to proposed labeling edits. Sarepta acknowledges clarification, understands, and promises to incorporate edits to the response

Date	Submission Activity Name	Application	Summary
			draft
7/31/2019	[REDACTED]-srpt-email-fda-4053-nda211970-proposed-labeling-revision.pdf	NDA 211970	Sarepta sent FDA notification that a submission was sent containing proposed labeling after incorporating edits from agency
7/31/2019	[REDACTED]-srpt-email-fda-4053-nda211970-proposed-labeling-text.pdf	NDA 211970	Sarepta sent FDA MS word version of proposed labeling after incorporating edits from agency, because the agency says it received the submission but could not locate the proposed labeling text and requested a MS word version be sent via email
7/31/2019	[REDACTED]-fda-email-[REDACTED]-4053-ind119982-fda-validation-comments.pdf	IND 119982	Sarepta's confirmation of receiving feedback and concerns on validation report
8/1/2019	[REDACTED]-fda-email-4053-nda211970-fda-request-labeling-revision.pdf	NDA 211970	Thank you. We will update the submission appropriately.
8/2/2019	[REDACTED]-srpt-email-fda-4053-nda211970-labeling-revision.pdf	NDA 211970	As a follow-up to the below communication, today we resubmitted the labeling revision document. The document is the same one we sent by email on Wednesday.
8/5/2019	[REDACTED]-fda-email-4053-nda211970-fda-request-for-labeling-info.pdf	NDA 211970	Ongoing labeling negotiations with FDA for 4053 NDA: Reference is made to pending NDA 211970 for golodirsen submitted on December 19, 2018; We have the following request for information. We ask for a response by COB Tuesday, 8/6/19; [REDACTED]

Date	Submission Activity Name	Application	Summary
8/6/2019	 -fda-email-4053-nda211970-fda-request-for-information-pmr.pdf	NDA 211970	<p>Discussion regarding draft proposed PMC, PMR: Please provide milestone dates and confirm your agreement with suggested milestone dates for golodirsen PMRs that would be imposed if the drug were to be approved. Propose milestone dates for PMRs #1-3 for the clinical study. Please clarify the clinical data that you propose to support PMRs #1-3. If the protocols have already been submitted and agreed upon, please let us know and use the submission dates for the milestone dates. Provide these dates by Thursday, August 8, 2019.</p> 

Date	Submission Activity Name	Application	Summary
			
8/7/2019	 -srpt-email-fda-4053-nda211970-pmr-rfi.pdf	NDA 211970	Sarepta's response to PMR RFI (06 Aug 2019); Attached is our response to the below request as a reference. We will formally submit later today.
8/12/2019	 -fda-email-4053-nda211970-pmr-comments.pdf	NDA 211970	Sarepta confirms receipt of PMR comments that require follow-up
8/12/2019	 -fda-email-4053-nda211970-fda-request-telecon.pdf	NDA 211970	FDA request for tentative telecon meeting about immunogenicity and clinical related questions
8/13/2019	 -srpt-email-fda-4053-nda211970-rir-pmr.pdf	NDA 211970	Sarepta's informal response to a request for information regarding the PMR, with a formal submission to follow
8/13/2019	 -srpt-email-fda-4053-nda211970-draft approval-press-release.pdf	NDA 211970	Sarepta confirming that because all comments from the Division on the draft label had been accepted, would there be questions and concerns regarding the planned press release in order to align the release of the final label with the press release
8/13/2019	 -fda-email-4053-nda211970-fda-proposed-labeling.pdf	NDA 211970	Sarepta's follow-up to FDA's proposed edits , letting the agency know that all edits have been reviewed and accepted
8/13/2019	 -fda-email-4053-nda211970-fda-proposed-labeling-text.pdf	NDA 211970	Sarepta confirms receipt of proposed PI edits with the intent to follow-up
8/14/2019	 -srpt-email-fda-4053-nda211970-request-for-advisory-	NDA 211970	Confirmation of receipt of FDA Letter in response to request to

Date	Submission Activity Name	Application	Summary
	comments.pdf		OPDP advisory comments
8/14/2019	██████-srpt-email-fda-4053-nda211970-response-proposed-pmr.pdf	NDA 211970	Attached reference to a request for response
8/14/2019	██████-fda-email-4053-nda211970-proposed-pmr.pdf	NDA 211970	Sarepta confirming receipt of question regarding PMR ██████ with intent on replying after internal discussions
8/14/2019	██████-srpt-email-fda-4053-nda211970-pmr-██████-feedback.pdf	NDA 211970	Sarepta's response to the FDA's questions about PMR ██████
8/14/2019	██████-fda-email-4053-fda-proposed-pmr-██████-nda211970-receipt-confirmation.pdf	NDA 211970	FDA Confirmation of receiving SRPT response to request, which we will formally submit to the NDA. One clarification as a follow-up to the teleconference related to the dates for PMR ██████
8/14/2019	██████-fda-email-4053-fda-proposed-pmr-██████-nda211970.pdf	NDA 211970	FDA following up to telecon, FDA proposed PMR ██████ if the drug were to be approved.
8/14/2019	██████-fda-email-4053-fda-proposed-pmr-nda211970.pdf	NDA 211970	FDA confirmation of receipt of attachments clarifying SRPT thinking related to PMRs ██████ after discussion about PMRs ██████
8/15/2019	██████-srpt-email-fda-nda211970-proposed-labeling-correction-sq0039.pdf	NDA 211970	Sarepta notifying FDA about an error in the final label submitted in sequence 0039
8/15/2019	██████-fda-email-4053-fda-proposed-labeling-text-nda211970.pdf	NDA 211970	FDA Confirmation of SRPT notification that there was an error in the final label submitted per the below email and with sequence 0039
8/19/2019	██████-fda-email-4053-fda-action-letter-nda211970.pdf	NDA 211970	FDA informing SRPT to please submit request for a Post-Action meeting/teleconference
8/19/2019	██████-fda-email-4053-fda-action-letter-nda211970-with-attachment.pdf	NDA 211970	FDA sending an electronic copy of the Agency's action letter for NDA 211970
8/20/2019	██████-srpt-email-fda-response-to-crl-meeting-request.pdf	NDA 211970	Sarepta's acceptance of a teleconference meeting invite by the FDA CDER Division of Neurology to discuss the action letter Sarepta received on 8/19/19
8/20/2019	██████-fda-email-4053-fda-action-letter-nda211970.pdf	NDA 211970	FDA follow-up to 19Aug19 request for an informal teleconference
8/23/2019	██████-fda-email-4053-fda-action-letter-nda211970.pdf	NDA 211970	FDA Confirming dial-in information and FDA attendee list
8/23/2019	██████-srpt-email-fda-4053-fda-action-letter-nda211970.pdf	NDA 211970	SRPT confirming FDA granting meeting request, and providing FDA with SRPT attendee list
8/26/2019	██████-srpt-email-fda-4053-teleconference-follow-up.pdf	NDA 211970	SRPT confirming time of meeting
8/29/2019	██████-fda-email-4053-golodirsen-nda211970-type-a-end-of-review-meeting-request.pdf	NDA 211970	FDA confirming that SRPT will be submitting a Type A End of Review meeting request
8/29/2019	██████-srpt-email-fda-4053-golodirsen-nda211970-type-a-end-of-review-meeting-request.pdf	NDA 211970	SRPT notifying FDA that SRPT will be submitting a Type A End of Review meeting request

Date	Submission Activity Name	Application	Summary
9/3/2019	██████-fda-email-4053-golodirsen-nda211970-type-a-end-of-review-meeting-request.pdf	NDA 211970	FDA acknowledge receipt of your 29Aug19, request for a Type A End of Review Meeting Request. FDA granted a face-to-face meeting and have scheduled the meeting
9/3/2019	██████-srpt-email-fda-4053-golodirsen-nda211970-type-a-end-of-review-meeting-request.pdf	NDA 211970	SRPT confirming receipt of FDA receipt acknowledgement of 29Aug19, request for a Type A End of Review Meeting Request. FDA granted a face-to-face meeting and have scheduled the meeting
9/4/2019	██████-fda-email-4053-golodirsen-nda211970-type-a-end-of-review-meeting-request-granted.pdf	NDA 211970	FDA letter formally granting your request for a Type A meeting and a Excel document for the list of attendees. FDA confirming receipt of completed Foreign Visitor Form
9/4/2019	██████-fda-email-4053-golodirsen-nda211970-type-a-end-of-review-meeting-request.pdf	NDA 211970	FDA requesting SRPT fill out foreign visitor form prior to meeting
9/10/2019	██████-fda-email-4053-fda-information-nda211970-type-a-meeting-prelim-comments.pdf	NDA 211970	FDA confirm receipt of SRPT final attendee list for your meeting and the foreign visitor form.
9/10/2019	██████-srpt-email-fda-4053-fda-information-nda211970-type-a-meeting-file-receipt-confirmation.pdf	NDA 211970	SRPT receipt confirmation of the Agency's preliminary responses to questions
9/12/2019	██████-fda-email-4053-golodirsen-nda211970-request-for-formal-dispute-resolution.pdf	NDA 211970	SRPT informed FDA of decision to submit a formal dispute resolution request.
9/12/2019	██████-fda-email-4053-final-participants-for-todays-meeting.pdf	NDA 211970	FDA ack of SRPT update to meeting attendee list
9/12/2019	██████-srpt-email-fda-4053-final-participants-for-todays-meeting.pdf	NDA 211970	SRPT updating meeting attendee list
9/13/2019	██████-fda-email-4053-golodirsen-eor-meeting.pdf	NDA 211970	FDA confirming receipt of document which contains introductory remarks and the Sarepta positions shared during the meeting for each of the identified issues
9/13/2019	██████-srpt-email-fda-4053-golodirsen-eor-meeting.pdf	NDA 211970	SRPT sending a document which contains introductory remarks and the Sarepta positions shared during the meeting for each of the identified issues
9/16/2019	██████-fda-email-4053-golodirsen-nda211970-request-for-formal-dispute-resolution.pdf	NDA 211970	FDA confirmed receipt of FDRR Friday, Sept 13th.
9/19/2019	██████-fda-email-4053-golodirsen-nda211970-request-for-formal-dispute-resolution.pdf	NDA 211970	FDA informed SRPT that our submission met criteria for acceptance.
9/23/2019	██████-fda-email-4053-golodirsen-nda211970-request-for-formal-dispute-	NDA 211970	FDA will communicate a formal decision letter signed by ██████.

Date	Submission Activity Name	Application	Summary
	resolution.pdf		
9/26/2019	██████-fda-email-4053-nda211970-fdrr-meeting-scheduling-list-of-attendees.pdf	NDA 211970	FDA provided list of CDER participants.
9/26/2019	██████-fda-email-4053-nda211970-fdrr-meeting-scheduling.pdf	NDA 211970	FDA scheduled f2f with FD RR for NDA 211970 on Oct 9th, 2019
9/26/2019	██████-srpt-email-fda-4053-nda211970-fdrr-meeting-scheduling.pdf	NDA 211970	SRPT confirmed team available for a meeting on 9Oct2019 to meet with FDA and discuss the issues involved in appeal.
9/27/2019	██████-fda-email-4053-nda211970-fdrr-ack-letter-attachment.pdf	NDA 211970	FDA provided copy of FD RR acknowledgement letter.
9/27/2019	██████-srpt-email-fda-4053-nda211970-fdrr-receipt-confirmation.pdf	NDA 211970	SRPT confirm receipt of FD RR acknowledgment letter and request an agenda for the meeting on 09Oct2019
9/30/2019	██████-fda-email-nda211970-fdrr.pdf	NDA 211970	FDA provided list of questions ██████ would like to discuss in f2f meeting 09Oct2019
9/30/2019	██████-srpt-email-fda-4053-nda211970-fdrr-foreign-visitor-form-attendees-list.pdf	NDA 211970	SRPT provided visitor attendees for f2f meeting at FDA on 09Oct2019
10/1/2019	██████-fda-email-4053-nda211970-fdrr.pdf	NDA 211970	FDA confirm receipt of SRPT meeting attendee list.
10/3/2019	██████-fda-email-4053-nda211970-fdrr.pdf	NDA 211970	FDA confirmed receipt of SRPT attendee list.
10/3/2019	██████-fda-email-4053-fda-information-nda211970-minutes.pdf	NDA 211970	FDA sending a courtesy copy of meeting minutes for 12Sep19 meeting
10/7/2019	██████-fda-email-4053-fdrr-meeting-rescheduling-confirmation-for-nda211970.pdf	NDA 211970	FDA rescheduled FD RR meeting to Oct 17,2019.
10/7/2019	██████-srpt-email-fda-4053-fdrr-meeting-rescheduling-confirmation-for-nda211970.pdf	NDA 211970	SRPT confirm team available for the updated meeting date at FDA on 17Oct2019
10/9/2019	██████-fda-email-4053-nda211970-fdrr-attendee-list-confirmation.pdf	NDA 211970	FDA confirm receipt of new attendees
10/9/2019	██████-srpt-email-fda-4053-nda211970-fdrr-updated-sarepta-meeting-attendee-list.pdf	NDA 211970	SPRT provided 2 potential participants, subject to chanfe once agend received.
10/15/2019	██████-srpt-email-fda-4053-nda211970-fdrr-updated-sarepta-meeting-attendee-list.pdf	NDA 211970	SRPT provided updated attendee list to FDA and promise slides by email prior to the meeting.
10/17/2019	██████-fda-email-4053-nda211970-fdrr-receipt-confirmation.pdf	NDA 211970	FDA confirm receipt of slides SRPT provided for meeting.
10/17/2019	██████-fda-email-4053-so-great-to-meet-you-today.pdf	NDA 211970	FDA wish safe travels and will work with ██████ to get SRPT and interim response.
10/17/2019	██████-srpt-email-fda-4053-nda211970-fdrr-meeting-slides.pdf	NDA 211970	SRPT provide presentation slides to FDA
10/21/2019	██████-fda-email-4053-fdrr-meeting-follow-up-with-attachment.pdf	NDA 211970	FDA provided courtesy copy of interim IR.
10/21/2019	██████-fda-email-4053-fdrr-meeting-follow-up.pdf	NDA 211970	FDA advise SRPT to wait for formal IR nd to send response

Date	Submission Activity Name	Application	Summary
			formally to NDA.
10/21/2019	██████-srpt-email-fda-fdrr-meeting-follow-up-receipt-confirmation.pdf	NDA 211970	SRPT confirm receipt of courtesy copy of interim IR.
10/21/2019	██████-srpt-email-fda-4053-fdrr-meeting-follow-up-clarification-thanks.pdf	NDA 211970	SRPT thanks to FDA for clarification that a formal IR will be sent.
10/21/2019	██████-srpt-email-fda-fdrr-meeting-follow-up-clarification-request.pdf	NDA 211970	SRPT asks for clarity on process of RFI and how response should be submitted.
10/24/2019	██████-fda-email-fdrr-meeting-follow-up.pdf	NDA 211970	FDA understands clarification provided by SRPT regarding FDA clarification request on articles - if they would be considered new information as publication dates or after date of CRL.
10/24/2019	██████-fda-email-4053-fdrr-meeting-follow-up-to-conversation.pdf	NDA 211970	FDA request clarification on articles would be considered new information as publication dates or after date of CRL.
10/24/2019	██████-srpt-email-fda-4053-fdrr-meeting-follow-up-response-to-information-request.pdf	NDA 211970	SRPT provided a courtesy copy of response to the information request from ██████
10/25/2019	██████-fda-email-4053-fdrr-meeting-follow-up.pdf	NDA 211970	FDA thank SRPT for courtesy copy of our responses to the information request from ██████
11/18/2019	██████-fda-email-4053-nda211970-fdr-meeting-minutes.pdf	NDA 211970	FDA provided SRPT courtesy copy of the FDR meeting minutes for NDA 211970.
11/18/2019	██████-srpt-email-fda-4053-nda211970-fdr-meeting-minutes.pdf	NDA 211970	SRPT confirm receipt of FDR meeting minutes for NDA 211970.
11/20/2019	██████-fda-email-4053-nda211970-fdr-meeting-minutes-response-confirmation.pdf	NDA 211970	FDA clarify the response to SRPT would be 30 (business) days from actual IR.
11/25/2019	██████-fda-email-4053-nda211970-golodirsens-crl-fdr.pdf	NDA 211970	FDA confirming time of call with SRPT
11/25/2019	██████-fda-email-4053-nda211970-golodirsens-crl-fdr-call-reschedule.pdf	NDA 211970	FDA rescheduling call with SRPT
11/25/2019	██████-fda-email-4053-nda211970-golodirsens-crl-fdr-email-receipt.pdf	NDA 211970	FDA confirming receipt of SRPT scheduling of phone call
11/25/2019	██████-fda-email-4053-nda211970-golodirsens-crl-fdr-call-schedule.pdf	NDA 211970	FDA confirming receipt of email. Scheduling a call
11/25/2019	██████-srpt-email-fda-4053-nda211970-golodirsens-crl-fdr.pdf	NDA 211970	SRPT confirming availability for scheduled call with FDA. SRPT providing dial-in info to FDA
11/25/2019	██████-srpt-email-fda-4053-nda211970-golodirsens-crl-fdr-complete-response-to-crl-post-appeal.pdf	NDA 211970	SRPT providing FDA with two documents prior to call. 1. Proposed new draft final labeling 2. Draft cover letter for the submission outlining the content
11/26/2019	██████-fda-email-4053-nda211970-fdr-response.pdf	NDA 211970	FDA responds to SRPT informing FDA the details of the clarification of resubmission process are being

Date	Submission Activity Name	Application	Summary
			worked through
11/26/2019	██████-fda-email-4053-nda211970-fdr-response-about-timing-and-logistics.pdf	NDA 211970	FDA available to discuss terms of re-submitting and logics and timing.
11/26/2019	██████-fda-email-4053-golodirsen-resubmission.pdf	NDA 211970	FDA confirming 356h form looks good.
11/26/2019	██████-fda-email-4053-golodirsen resubmission-correction.pdf	NDA 211970	FDA notifying SRPT of corrected date of FDR meeting
11/26/2019	██████-fda-email-4053-golodirsen-nda211970-proprietary-name-resubmission-received.pdf	NDA 211970	FDA receipt of receiving SRPT follow-up to resubmission
11/26/2019	██████-fda-email-4053-golodirsen-resubmission-link-to-previous-materials-request.pdf	NDA 211970	FDA telling SRPT to provide links to the previous submitted materials
11/26/2019	██████-fda-email-4053-golodirsen-resubmission-cover-letter-complete-response-to-crl-post-appeal-draft.pdf	NDA 211970	FDA sending SRPT labeling suggestions for resubmission
11/26/2019	██████-fda-email-4053-golodirsen-appeal-granted-and-resubmission.pdf	NDA 211970	FDA notifying SRPT that information have been shared with ██████
11/26/2019	██████-srpt-email-fda-4053-golodirsen-resubmission.pdf	NDA 211970	SRPT asking for advice on 356h form
11/26/2019	██████-srpt-email-fda-4053-golodirsen-resubmission-confirmation-request.pdf	NDA 211970	SRPT asking for FDA to confirm that documents should be resubmitted instead of just providing links
11/26/2019	██████-srpt-email-fda-4053-golodirsen-appeal-granted-and-resubmission.pdf	NDA 211970	SRPT asking FDA if agency prefers links to previously submitted documents if possible
11/27/2019	██████-srpt-email-fda-4053-golodirsen-resubmission.pdf	NDA 211970	Informal notification from SRPT to FDA that submissions went in.
11/29/2019	██████-fda-email-4053-golodirsen-resubmission-receipt-confirmation.pdf	NDA 211970	FDA notifying SRPT that the submissions have been received via ESG
11/29/2019	██████-srpt-email-fda-4053-golodirsen-resubmission.pdf	NDA 211970	SRPT confirming FDA notification that the submissions were received via ESG
12/2/2019	██████-fda-email-40543-fda-information-request-nda211970.pdf	NDA 211970	FDA request for information regarding NDA 211970 in resubmission safety update submitted 27No2019.
12/3/2019	██████-fda-email-4053-fda-proposed-pmrs-nda211970.pdf	NDA 211970	FDA provided postmarketing requirements for the golodirsen NDA.
12/3/2019	██████-srpt-email-fda-4053-fda-proposed-pmrs-nda211970.pdf	NDA 211970	SRPT notifying FDA the proposed PMRs have been reviewed
12/3/2019	██████-srpt-email-fda-4053-fda-information-request-nda211970.pdf	NDA 211970	SRPT providing FDA courtesy copy of the response being submitted
12/4/2019	██████-srpt-email-fda-4053-fda-proposed-pmrs-nda211970.pdf	NDA 211970	SRPT notifying FDA of a formal submission
12/6/2019	██████-fda-email-4053-fda-proposed-labeling-text-nda211970.pdf	NDA 211970	FDA proposed labeling text for NDA 211970
12/6/2019	██████-srpt-email-fda-4053-fda-proposed-labeling-text-	NDA 211970	SRPT providing courtesy copies of proposed final labeling to FDA

Date	Submission Activity Name	Application	Summary
	nda211970.pdf		
12/6/2019	██████-srpt-email-fda-4053-fda-proposed-labeling-text-nda211970-receipt-confirmation.pdf	NDA 211970	SRPT confirming receipt of proposed labeling edits from FDA
12/6/2019	██████-srpt-email-fda-4053-fda-proposed-labeling-text-nda211970(2).pdf	NDA 211970	SRPT providing courtesy copies of proposed final labeling to FDA
12/6/2019	██████-srpt-email-fda-4053-fda-proposed-labeling-text-nda211970-confirm-receipt.pdf	NDA 211970	SRPT confirming receipt of proposed labeling edits from FDA
12/9/2019	██████-fda-email-4053-request-for-information-fda-proposed-labeling-text-nda-211970.pdf	NDA 211970	SRPT confirm receipt of proposed labeling text for NDA 211970
12/9/2019	██████-fda-email-4053-request-for-information-fda-proposed-labeling-text-nda211970.pdf	NDA 211970	FDA asking for SRPT to provide a response to an information request
12/9/2019	██████-srpt-email-fda-4053-request-for-information-fda-proposed-labeling-text-nda211970.pdf	NDA 211970	SRPT confirming receipt of email from FDA about not submitting labeling until there is an agreed-upon PI
12/9/2019	██████-srpt-email-fda-4053-fda-proposed-labeling-text-nda211970-rfi-renal-tox-labeling.pdf	NDA 211970	SRPT response to an FDA information request
12/9/2019	██████-srpt-email-fda-4053-fda-proposed-labeling-text-nda211970-rfi-response.pdf	NDA 211970	SRPT thanking FDA for clarification. SRPT notifying FDA that submission will only include response to questions
12/9/2019	██████-srpt-email-fda-4053-request-for-information-fda-proposed-labeling-text-nda211970-confirmation.pdf	NDA 211970	SRPT confirm receipt of information request.
12/9/2019	██████-fda-email-4053-fda-proposed-labeling-text-nda211970.pdf	NDA 211970	FDA confirming SRPT notification of a formal submission of labeling. FDA tellign SRPT to wait until there is an agreed-upon PI
12/10/2019	██████-srpt-email-fda-4053-fda-proposed-labeling-text-nda211970-fda-edits.pdf	NDA 211970	SRPT sending FDA updated proposed PI
12/10/2019	██████-fda-email-4053-fda-proposed-labeling-text-nda211970.pdf	NDA 211970	FDA confirming receipt of updated proposed PI
12/11/2019	██████-fda-email-4053-request-for-information-fda-proposed-labeling-text-nda211970.pdf	NDA 211970	FDA instruct SRPT to respond to the proposed labeling via email.
12/11/2019	██████-request-for-information-fda-proposed-labeling-text-nda211970.pdf	NDA 211970	FDA request for information regarding proposed renal monitoring in labeling.
12/11/2019	██████-srpt-email-fda-4053-fda-proposed-labeling-text-nda211970.pdf	NDA 211970	SRPT confirming receipt of FDA notification that the agreed-upon labeling can be formally submitted
12/11/2019	██████-srpt-email-fda-4053-request-for-information-fda-proposed-labeling-text-nda211970.pdf	NDA 211970	SRPT asking FDA if agency will have it's own press release about approval
12/11/2019	██████-srpt-email-fda-4053-call-request-for-information-fda-proposed-labeling-text-nda211970.pdf	NDA 211970	SRPT request for phone call with FDA

Date	Submission Activity Name	Application	Summary
12/11/2019	██████-srpt-email-fda-request-for-information-confirmation-fda-proposed-labeling-text-nda211970.pdf	NDA 211970	SRPT asking FDA if proposed labeling can be sent via email or if a formal submission is needed
12/11/2019	██████-srpt-email-fda-4053-fda-proposed-labeling-text-nda211970-receipt-confirmation.pdf	NDA 211970	SRPT confirming receipt of and agreement to FDA proposed labeling text.
12/11/2019	██████-srpt-email-fda-4053-fda-proposed-labeling-text-nda211970-fda-edits.pdf	NDA 211970	SRPT proving FDA with revised proposed labeling incorporating response to FDA information request
12/11/2019	██████-srpt-email-fda-4053-fda-proposed-labeling-text-nda211970-confirm-receipt-request.pdf	NDA 211970	SRPT confirming FDA information request
12/11/2019	██████-fda-email-4053-fda-proposed-labeling-text-nda211970-fda-edits.pdf	NDA 211970	FDA sending SRPT FDA proposed labeling text, dated 11Dec2019 for golodirsén
12/11/2019	██████-fda-email-4053-fda-proposed-labeling-text-nda211970-formally-submit-labeling.pdf	NDA 211970	FDA notifying SRPT to formally submit the agreed-upon labeling
12/12/2019	██████-fda-email-4053-agreed-upon-pi-fda-proposed-labeling-text-nda211970.pdf	NDA 211970	FDA provided clean version of the golodirsén agreed-upon labeling dated 11Dec2019.
12/12/2019	NDA 211970 Approval	NDA 211970	

14481558.1



UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22314-1450
www.uspto.gov

Food and Drug Administration
CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51 Room 6250
Silver Spring MD 20993-0002

MAR 11 2020

Attention: Beverly Friedman

The attached application for patent term extension of U.S. Patent No. 9,994,851 was filed on February 4, 2020, under 35 U.S.C. § 156. Please note that patent term extension applications for U.S. Patent No. 9,024,007, U.S. Patent No. 10,227,590, U.S. Patent No. 10,266,827, U.S. Patent No. 10,421,966, and U.S. Patent No. RE47,691 for new drug application (NDA) No. 211970 for the drug product VYONDYS 53[®] (golodirsen) were filed concurrently, pursuant to the provisions of 37 C.F.R. § 1.785.

The assistance of your Office is requested in confirming that the product identified in the application, VYONDYS 53[®] (golodirsen), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period beginning on the date the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156.

Inquiries regarding this communication should be directed to the undersigned at (571) 272-0909 (telephone) or (571) 273-0909 (facsimile) or by e-mail at ali.salimi@uspto.gov.

A handwritten signature in dark ink, appearing to read "Ali Salimi", written over a horizontal line.

Ali Salimi
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Eric K. Steffe
Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue, N.W.
Washington, D.C. 20005

SRPT-VYDS-0005229



**U.S. FOOD & DRUG
ADMINISTRATION**

Re: VYONDYS 53
Patent Nos. 9,994,851; 9,024,007;
10,227,590; 10,266,827;
10,421,966; and RE47691
Docket Nos. FDA-2020-E-1318;
FDA-2020-E-1319;
FDA-2020-E-1320;
FDA-2020-E-1321;
FDA-2020-E-1322;
and FDA-2020-E-1323

The Honorable Andrei Iancu
Under Secretary of Commerce for Intellectual Property
Director, United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

JUL 14 2020

Dear Director Iancu:

This is concerning the applications for patent term extension for U.S. Patent Nos. 9,994,851; 9,024,007; 10,227,590; 10,266,827; 10,421,966; and RE47691 filed by The University of Western Australia, under 35 U.S.C. 156. The human drug product claimed by the patents is VYONDYS 53 (golodirsen), which was assigned new drug application (NDA) No. 211970.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. 156(a)(4). Our records also indicate that it represents the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. 156(f)(1).

NDA 211970 was approved on December 12, 2019, which makes the submission of the patent term extension application on February 4, 2020, timely within the meaning of 35 U.S.C. 156(d)(1).

Should you conclude that the subject patent is eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. 156(d)(2)(A) we will then determine the applicable regulatory review period, publish the determination in the *Federal Register*, and notify you of our determination.

U.S. Food and Drug Administration
10903 New Hampshire Avenue

Washington, DC 20205

Silver Spring, MD 20910

2020-07-14

SRPT-VYDS-0005230

VYONDYS 53

Patent No. 9,994,851; 9,024,007; 10,227,590; 10,266,827; 10,421,966; and RE47691

Page 2

Please let me know if we can be of further assistance.

Sincerely yours,

A handwritten signature in black ink, reading "Patrizia Cavazzoni". The signature is fluid and cursive, with the first name "Patrizia" and last name "Cavazzoni" clearly distinguishable.

Patrizia Cavazzoni, M.D., Acting Director
Center for Drug Evaluation and Research
Food and Drug Administration

cc: Eric K. Steffe
Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue, N.W.
Washington, DC 20005



Re: VYONDYS 53
Patent Nos. 9,994,851; 9,024,007;
10,227,590; 10,266,827;
10,421,966; and RE47691
Docket Nos. FDA-2020-E-1318;
FDA-2020-E-1319;
FDA-2020-E-1320;
FDA-2020-E-1321;
FDA-2020-E-1322;
and FDA-2020-E-1323

The Honorable Andrei Iancu
Under Secretary of Commerce for Intellectual Property
Director, United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

JUL 14 2020

Dear Director Iancu:

This is concerning the applications for patent term extension for U.S. Patent Nos. 9,994,851; 9,024,007; 10,227,590; 10,266,827; 10,421,966; and RE47691 filed by The University of Western Australia, under 35 U.S.C. 156. The human drug product claimed by the patents is VYONDYS 53 (golodirsen), which was assigned new drug application (NDA) No. 211970.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. 156(a)(4). Our records also indicate that it represents the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. 156(f)(1).

NDA 211970 was approved on December 12, 2019, which makes the submission of the patent term extension application on February 4, 2020, timely within the meaning of 35 U.S.C. 156(d)(1).

Should you conclude that the subject patent is eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. 156(d)(2)(A) we will then determine the applicable regulatory review period, publish the determination in the *Federal Register*, and notify you of our determination.

U.S. Food and Drug Administration
10903 New Hampshire Avenue

Washington, DC 20892
202-201-3000
www.fda.gov

VYONDYS 53

Patent No. 9,994,851; 9,024,007; 10,227,590; 10,266,827; 10,421,966; and RE47691

Page 2

Please let me know if we can be of further assistance.

Sincerely yours,

A handwritten signature in black ink, reading "Patrizia Cavazzoni". The signature is fluid and cursive, with the first name "Patrizia" and last name "Cavazzoni" clearly distinguishable.

Patrizia Cavazzoni, M.D., Acting Director
Center for Drug Evaluation and Research
Food and Drug Administration

cc: Eric K. Steffe
Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue, N.W.
Washington, DC 20005



UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22314-1450
www.uspto.gov

Food and Drug Administration
CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51 Room 6250
Silver Spring MD 20993-0002

March 5, 2021

Attention: Beverly Friedman

Dear Sir:

Transmitted herewith is a copy of the application for patent term extension of U.S. Patent No. 9,994,851. The application was filed on February 4, 2020, under 35 U.S.C. § 156. Please note that patent term extension applications for U.S. Patent No. 9,024,007, U.S. Patent No. 10,227,590, U.S. Patent No. 10,266,827, U.S. Patent No. 10,421,966, and U.S. Patent No. RE47,691 based on the regulatory review of NDA 211970 for the product VYONDYS 53[®] (golodirsen) were filed concurrently, pursuant to the provisions of 37 C.F.R. § 1.785.

The patent claims a product which has been subject to review under the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product. Subject to final review, the subject patent is considered to be eligible for patent term extension. Thus, a determination by your office of the applicable regulatory review period is necessary. Accordingly, notice and a copy of the application are provided pursuant to 35 U.S.C. § 156(d)(2)(A).

Inquiries regarding this communication should be directed to the undersigned at (571) 272-0909 (telephone) or by e-mail to ali.salimi@uspto.gov.

/Ali Salimi/

Ali Salimi
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Eric K. Steffe
Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue, N.W.
Washington, D.C. 20005

RE: VYONDYS 53[®] (golodirsen)
Docket No. FDA-2020-E-1318



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE	REQUEST ID
15/705,172	09/14/2017	Stephen Donald WILTON	4140.01500A9	135376

Acknowledgement of Loss of Entitlement to Entity Status Discount

The entity status change request below filed through Private PAIR on 03/30/2021 has been accepted.

CERTIFICATIONS:

Change of Entity Status:

☒ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be notification of loss of entitlement to small or micro entity status, as applicable.

This portion must be completed by the signatory or signatories making the entity status change in accordance with 37 CFR 1.4(d)(4).

Signature:	/Christopher Verni, Reg. No. 48322/
Name:	Christopher Verni
Registration Number:	48322

AO 120 (Rev. 08/10)

TO: Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
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In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been
 filed in the U.S. District Court _____ for the District of Delaware _____ on the following

☐ Trademarks or ☒ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED 7/13/2021	U.S. DISTRICT COURT for the District of Delaware
PLAINTIFF NIPPON SHINYAKU CO., LTD.		DEFENDANT SAREPTA THERAPEUTICS, INC.
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 9,708,361	7/18/2017	Nippon Shinyaku
2 10,385,092	8/20/2019	Nippon Shinyaku
3 10,407,461	9/10/2019	Nippon Shinyaku
4 10,487,106	11/26/2019	Nippon Shinyaku
5 10,647,741	5/20/2020	Nippon Shinyaku

Additional patents including by initial pleading listed below.

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED 7/13/2021	INCLUDED BY <input type="checkbox"/> Amendment <input type="checkbox"/> Answer <input type="checkbox"/> Cross Bill <input checked="" type="checkbox"/> Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 10,662,217	5/26/2020	Nippon Shinyaku
2 10,683,322	6/16/2020	Nippon Shinyaku
3 9,994,851	6/12/2018	Sarepta Therapeutics, Inc.
4 10,227,590	3/12/2019	Sarepta Therapeutics, Inc.
5 10,266,827	4/23/2019	Sarepta Therapeutics, Inc.

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
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Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
 Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

SRPT-VYDS-0005236

Re: VYONDYS 53
Patent Nos.: 9,024,007; 9,994,851;
10,227,590; 10,266,827;
10,421,966; and RE47,691
Docket Nos.: FDA-2020-E-1318;
FDA-2020-E-1319; FDA-2020-E-1320;
FDA-2020-E-1321; FDA-2020-E-1322;
and FDA-2020-E-1323

The Honorable Drew Hirshfeld
Acting Under Secretary of Commerce for Intellectual Property and
Director, United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

OCT 22 2021

Dear Director Hirshfeld:

This is in regard to the applications for patent term extension for U.S. Patent Nos. 9,024,007; 9,994,851; 10,227,590; 10,266,827; 10,421,966; and RE47,691, filed by The University of Western Australia, under 35 U.S.C. 156 et seq. The U.S. Food and Drug Administration (FDA) has reviewed the dates contained in the applications and has determined the regulatory review period for VYONDYS 53 (golodirsen), the human drug product claimed by the patents.

The total length of the regulatory review period for VYONDYS 53 is 1,833 days. During this time, 1,474 days occurred during the testing phase and 359 days occurred during the approval phase. These periods of time were derived from the following dates:

1. The date this biologic product became effective according to an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)(21 U.S.C. 355(i)):
December 7, 2014.

The applicant claims January 28, 2016, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND's first effective date was December 7, 2014, which was thirty days after FDA receipt of the IND.

2. The date the application was initially submitted with respect to the new drug application under section 505 of the Federal Food, Drug, and Cosmetic Act: December 19, 2018.

U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 51, Room 6250
Silver Spring, MD 20993-0002
www.fda.gov

USPTO - VYONDYS 53

U.S. Patent Nos. 9,024,007; 9,994,851; 10,227,590; 10,266,827; 10,421,966; and RE47,691

Page | 2

FDA has verified the applicant's claim that the new drug application (NDA) for VYONDYS 53 (NDA 211970) was initially submitted on December 19, 2018.

3. The date the application was approved: December 12, 2019.

FDA has verified the applicant's claim that NDA 211970 was approved on December 12, 2019.

This determination of the regulatory review period by FDA does not take into account the effective date of the patent, nor does it exclude one-half of the testing phase as required by 35 U.S.C. section 156(c)(2).

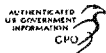
Please let me know if we can be of further assistance.

Sincerely yours,



Patrizia Cavazzoni, M.D., Director
Center for Drug Evaluation and Research
Food and Drug Administration

cc: Eric K. Steffe
Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue, N.W.
Washington, DC 20005



60256

Federal Register / Vol. 86, No. 208 / Monday, November 1, 2021 / Notices

we will also code and compare responses across types of drug names.

FDA estimates the burden of this collection of information as follows:

TABLE 1—ESTIMATED ANNUAL REPORTING BURDEN¹

Activity	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
General Consumer Population					
Pretest 1 screener (assumes 80% eligible)	22	1	22	0.08 (5 minutes)	1.8
Pretest 1 survey	15 + 10% ² = 17	1	15 + 10% ² = 17	0.33 (20 minutes)	5.6
Pretest 2 screener (assumes 80% eligible)	22	1	22	0.08 (5 minutes)	1.8
Pretest 2 survey	15 + 10% ² = 17	1	15 + 10% ² = 17	0.33 (20 minutes)	5.6
Main study screener completes (assumes 80% eligible)	413	1	413	0.08 (5 minutes)	33
Main study survey completes	300 + 10% ² = 330	1	300 + 10% ² = 330	0.33 (20 minutes)	108.9
PCP Population					
Pretest 1 screener (assumes 30% eligible)	57	1	57	0.08 (5 minutes)	4.6
Pretest 1 survey	15 + 10% ² = 17	1	15 + 10% ² = 17	0.33 (20 minutes)	5.6
Pretest 2 screener (assumes 30% eligible)	57	1	57	0.08 (5 minutes)	4.6
Pretest 2 survey	15 + 10% ² = 17	1	15 + 10% ² = 17	0.33 (20 minutes)	5.6
Main study screener completes (assumes 30% eligible)	1,100	1	1,100	0.08 (5 minutes)	88
Main study survey completes	300 + 10% ² = 330	1	300 + 10% ² = 330	0.33 (20 minutes)	108.9
Total	374

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

² As with most online and mail surveys, it is always possible that some participants are in the process of completing the survey when the target number is reached and that those surveys will be completed and received before the survey is closed out. To account for this, we have estimated approximately 10 percent overage for both samples in the study.

Dated: October 22, 2021.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2021-23731 Filed 10-29-21; 8:45 am]

BILLING CODE 4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket Nos. FDA-2020-E-1318, FDA-2020-E-1319, FDA-2020-E-1320, FDA-2020-E-1321, FDA-2020-E-1322, and FDA-2020-E-1323]

Determination of Regulatory Review Period for Purposes of Patent Extension; VYONDYS 53

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or the Agency) has determined the regulatory review period for VYONDYS 53 and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of applications to the Director of the U.S. Patent and Trademark Office (USPTO), Department of Commerce, for the extension of a

patent which claims that human drug product.

DATES: Anyone with knowledge that any of the dates as published (see **SUPPLEMENTARY INFORMATION**) are incorrect may submit either electronic or written comments and ask for a redetermination by January 3, 2022. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period by May 2, 2022. See "Petitions" in the **SUPPLEMENTARY INFORMATION** section for more information.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before January 3, 2022. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of January 3, 2022. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- **Federal eRulemaking Portal:** <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- **Mail/Hand Delivery/Courier (for written/paper submissions):** Dockets Management Staff (HFA-305), Food and

Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket Nos. FDA-2020-E-1318, FDA-2020-E-1319, FDA-2020-E-1320, FDA-2020-E-1321, FDA-2020-E-1322, and FDA-2020-E-1323 for "Determination of Regulatory Review Period for Purposes of Patent Extension; VYONDYS 53". Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- **Confidential Submissions**—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with § 10.20 (21 CFR 10.20) and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the

heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Beverly Friedman, Office of Regulatory Policy, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6250, Silver Spring, MD 20993, 301-796-3600.

SUPPLEMENTARY INFORMATION:

I. Background

The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) and the Generic Animal Drug and Patent Term Restoration Act (Pub. L. 100-670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug or biologic product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: a testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of USPTO may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA has approved for marketing the human drug product VYONDYS 53 (golodirsen). VYONDYS 53 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with VYONDYS 53. Continued approval for this indication may be

contingent upon verification of a clinical benefit in confirmatory trials. Subsequent to this approval, the USPTO received patent term restoration applications for VYONDYS 53 (U.S. Patent Nos. 9,024,007; 9,994,851; 10,227,590; 10,266,827; 10,421,966; and RE47,691) from The University of Western Australia, and the USPTO requested FDA's assistance in determining the patents' eligibility for patent term restoration. In a letter dated July 14, 2020, FDA advised the USPTO that this human drug product had undergone a regulatory review period and that the approval of VYONDYS 53 represented the first permitted commercial marketing or use of the product. Thereafter, the USPTO requested that FDA determine the product's regulatory review period.

II. Determination of Regulatory Review Period

FDA has determined that the applicable regulatory review period for VYONDYS 53 is 1,833 days. Of this time, 1,474 days occurred during the testing phase of the regulatory review period, while 359 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(i)) became effective:* December 7, 2014. The University of Western Australia claims that January 28, 2016, is the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND's first effective date was December 7, 2014, which was 30 days after FDA receipt of the IND.

2. *The date the application was initially submitted with respect to the human drug product under section 505 of the FD&C Act:* December 19, 2018. FDA has verified the applicant's claim that the new drug application (NDA) for VYONDYS 53 (NDA 211970) was initially submitted on December 19, 2018.

3. *The date the application was approved:* December 12, 2019. FDA has verified the applicant's claim that NDA 211970 was approved on December 12, 2019.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the USPTO applies several statutory limitations in its calculations of the actual period for patent extension. In its applications for patent extension, this applicant seeks 80 days, 124 days, 276 days, 454 days, or 888 days of patent term extension.

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III. Petitions

Anyone with knowledge that any of the dates as published are incorrect may submit either electronic or written comments and, under 21 CFR 60.24, ask for a redetermination (see **DATES**). Furthermore, as specified in § 60.30 (21 CFR 60.30), any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period. To meet its burden, the petition must comply with all the requirements of § 60.30, including but not limited to: must be timely (see **DATES**), must be filed in accordance with § 10.20, must contain sufficient facts to merit an FDA investigation, and must certify that a true and complete copy of the petition has been served upon the patent applicant. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Submit petitions electronically to <https://www.regulations.gov> at Docket No. FDA–2013–S–0610. Submit written petitions (two copies are required) to the Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Dated: October 22, 2021.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2021–23724 Filed 10–29–21; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2018–N–4130]

Agency Information Collection Activities; Proposed Collection; Comment Request; Recordkeeping Requirements for Microbiological Testing and Corrective Measures for Bottled Water

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is announcing an opportunity for public comment on the proposed collection of certain information by the Agency. Under the Paperwork Reduction Act of 1995 (PRA), Federal Agencies are required to publish notice in the **Federal Register** concerning each proposed collection of information, including each proposed extension of an

existing collection of information, and to allow 60 days for public comment in response to the notice. This notice solicits comments on the procedure by which both domestic and foreign bottled water manufacturers that sell bottled water in the United States maintain records of microbiological testing and corrective measures, in addition to existing recordkeeping requirements.

DATES: Submit either electronic or written comments on the collection of information by January 3, 2022.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before January 3, 2022. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of January 3, 2022. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

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Instructions: All submissions received must include the Docket No. FDA–2018–N–4130 for “Agency Information Collection Activities; Proposed Collection; Comment Request; Recordkeeping Requirements for Microbiological Testing and Corrective Measures for Bottled Water.” Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

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